

13 Oncologic Emergencies

N.-E.B. JACOBSEN, S.D.W. BECK, R.S. FOSTER

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13.1 Introduction

It has been estimated that genitourinary malignancies will account for 25% of new cancer diagnoses in the United States in 2005 (Jemal et al. 2005). While the incidence of many of these malignancies has increased over the past two decades, the mortality rates appear to be decreasing. Early cancer detection combined with improvements in surgical and nonsurgical oncologic therapy account for these trends. Although not common, newly diagnosed cancer patients occasionally present in an emergent, life-threatening manner that warrants immediate medical or surgical intervention. As the prevalence of genitourinary malignancies continues to expand, additional patients can be expected to develop disease or treatment-related complications. This chapter will serve to review the diagnosis and management of oncologic emergencies as they pertain to the urologist.

13.2 Spontaneous Perinephric Hemorrhage

Renal cell carcinoma (RCC) is the fourth most common genitourinary malignancy in the United States, with an estimated 36,000 new cases expected in 2005 (Jemal et al. 2005). In contrast to years past, the majority of cases are now diagnosed incidentally due to the widespread availability and performance of abdominal imaging. While presentation with the classic triad of flank pain, gross hematuria, and a palpable abdominal mass is now rare (Jayson and Sanders 1998), a small proportion of cases complicated by a spontaneous perinephric hemorrhage (SPH) will demonstrate one or all of these findings. It is difficult to estimate the true incidence of spontaneous tumor hemorrhage since SPH is not specific to RCC and most descriptions of SPH amount to case reports only. Nonetheless, this would appear to be an uncommon mode of presentation for RCC. Neovascularity and propensity for necrosis are possible explanations for tumor rupture and hemorrhage (Hora et al. 2004).

13.2.1

Background

Spontaneous perinephric hemorrhage represents a diagnostic and therapeutic challenge. Appropriate treatment depends on the hemodynamic stability of the patient and a correct determination of its cause. In light of its infrequent occurrence, management guidelines for SPH are based on data acquired through meta-analyses of case reports. Since 1933, four available meta-analyses have reviewed 448 cases of SPH, 165 of which took place after 1985 (Polkey and Vynalek 1933; McDougal et al. 1975; Cinman et al. 1985; Zhang et al. 2002). It appears that SPH occurs with equal frequency in males and females as well as in right and left kidneys. Flank or abdominal pain of acute onset is the most common presenting symptom (83%–100%) (Zhang et al. 2002; Pe-verzev et al. 2005). Interestingly, only a minority of SPH cases demonstrate gross or microscopic hematuria (0%–19%). Up to 11% present with signs and symptoms of hypovolemic shock indicative of a severe retroperitoneal hemorrhage. Numerous etiologies exist, the most common of which is neoplasm (57%–66%), benign or malignant, followed by vascular disease (17%–26%), idiopathic hemorrhage (6.7%), and infection (2.4%). Angiomyolipoma (AML) and RCC represent the most common benign and malignant neoplastic causes of SPH, accounting for 24%–33% and 30%–33% of all cases, respectively. With such disparate etiologic possibilities, accurate diagnosis is of the utmost importance to ensure appropriate treatment is provided.

Computed tomography (CT) with intravenous (i.v.) contrast is the imaging study of choice for SPH (Fig. 13.1). The diagnostic accuracy of CT for a perinephric hematoma approaches 100%, and the reported

sensitivity and specificity for identification of an underlying mass is 57% and 82%, respectively (Zhang et al. 2002). Contemporary series employing state-of-the-art CT imaging technology report up to 92% diagnostic accuracy for determination of the underlying cause of SPH (Sebastia et al. 1997). In contrast, the sensitivity and specificity of ultrasound (US) is 11% and 33%, respectively. Magnetic resonance imaging (MRI) is an appropriate substitute in cases where contraindications to i.v. contrast exist or CT is unavailable. Diagnostic arteriography is indicated if CT or MRI does not demonstrate a mass or if a vascular etiology is suspected (Zagoria et al. 1991). Bilateral SPH, reported in 3% of cases, suggests a vascular diagnosis such as polyarteritis nodosa (Zhang et al. 2002).

Identification of fat content (<10 Hounsfield Units) within a renal mass on CT, although not sensitive, is a highly specific finding for AML (Fig. 13.2) (Bosniak et

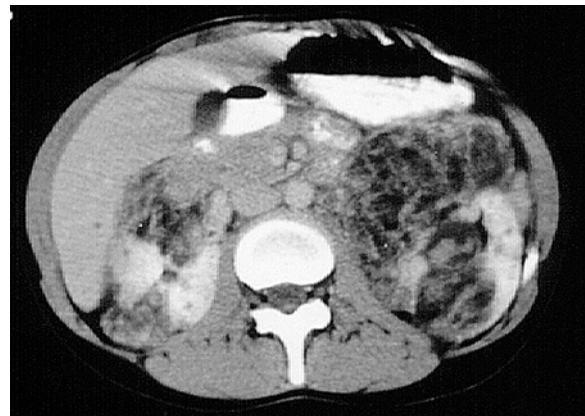


Fig. 13.2. Angiomyolipoma. CT demonstrating bilateral angiomyolipomas with characteristic fat attenuation

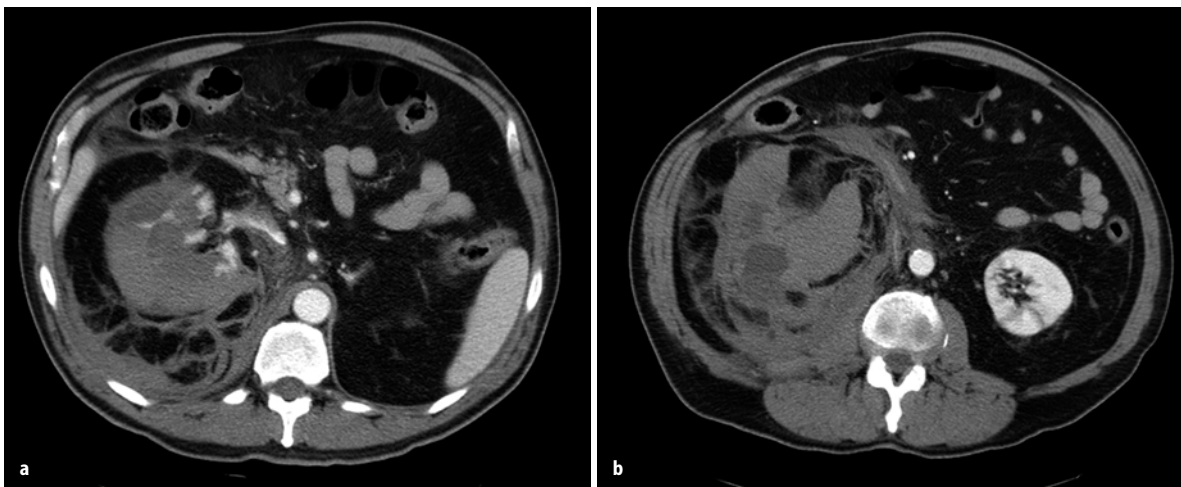


Fig. 13.1a, b. Spontaneous right hemorrhage. **a, b** Contrast-enhanced CT demonstrating right renal hemorrhage into perinephric space. No mass lesion is discernible. Patient was subsequently diagnosed with renovascular disease

al. 1988; Lemaitre et al. 1997). In contrast, any heterogeneous solid or cystic mass without fat should be regarded as RCC until proven otherwise. Of note, tumor size does correlate with risk of hemorrhage for AML; however, no such correlation has been shown for RCC (Zhang et al. 2002).

13.2.2

Evaluation

At the time of presentation, a thorough history, physical examination, and determination of hemodynamic stability should ensue. Given that flank pain arising from SPH is commonly confused with renal colic, a noncontrast CT of the abdomen and pelvis is often performed. In fact, a contrast-enhanced CT is the first-line study and should be obtained in the event that a non-contrast CT or US suggests the presence of a retroperitoneal hematoma. Laboratory studies should include a complete blood count (CBC), electrolytes, blood urea nitrogen (BUN), creatinine, and a coagulation profile.

13.2.3

Treatment

The management of SPH is similar to that of renal trauma wherein conservative measures are first-line and nephrectomy is reserved as an option of last resort (Santucci and Fisher 2005). Initial steps are directed toward maintaining hemodynamic support through i.v. hydration and blood and blood product replacement as necessary. Bed rest is instituted along with periodic monitoring of vital statistics and serum hemoglobin in those patients who are hemodynamically stable. Unstable patients or those in whom the hemoglobin continues to decrease despite repeated transfusions require diagnostic arteriography and selective embolization. Only patients who remain unstable or continue to bleed despite embolization need undergo open nephrectomy. Partial nephrectomy remains an option in the early period but should be restricted to patients with a solitary kidney or those with a small (<4 cm), easily identifiable exophytic mass whose hemodynamic parameters do not prohibit an extended procedure. Seven percent of patients with a renal mass in available series have undergone early partial nephrectomy in the setting of SPH (Zhang et al. 2002). Unfortunately, no data on local recurrence is available at this time.

Patients with hemodynamic stability including those responding to conservative measures, including embolization, require inpatient monitoring and symptomatic treatment only. Ambulation and subsequent hospital discharge can be initiated when vital signs and hemoglobin remain stable for 24 h and gross hematuria, if present, has resolved. Given the 25% risk of underlying malignancy, repeat abdominal imaging with

CT scan should be performed in 1–3 months (Zhang et al. 2002; Yip et al. 1998). If a mass suggestive of RCC is identified at presentation or in follow-up, definitive treatment can be performed on an elective basis.

13.3

Hypercalcemia of Malignancy

Hypercalcemia is the most common paraneoplastic syndrome of malignancy (Fojo 2005). Among genitourinary malignancies, it is most frequently identified in association with RCC (3%–25%) (Zekri et al. 2001; Walther et al. 1997; Papac and Poo-Hwu 1999; Skinner et al. 1971). In comparison, hypercalcemia is an uncommon manifestation of prostate cancer and transitional cell carcinoma (Coleman 1997). The incidence of hypercalcemia in RCC correlates with the stage of the primary tumor as well as with the presence or absence of bone metastases (Fahn et al. 1991). Hypercalcemia typically occurs late in the course of disease and has demonstrated independent significance as a poor prognostic factor in patients with advanced RCC (Motzer et al. 1999).

13.3.1

Pathophysiology

Two pathogenic mechanisms are involved in the generation of hypercalcemia: (1) focal osteolytic bone destruction secondary to bone metastases and (2) uncoupling of bone turnover secondary to tumor-secreted humoral factors. Focal bone destruction by metastases involves the paracrine secretion of various cytokines that stimulate local osteoclasts and inhibit osteoblasts. Although this mechanism certainly contributes to hypercalcemia, it appears that systemic factors play a more important role. Malignant hypercalcemia caused by the production of humoral factors is often referred to as humoral hypercalcemia of malignancy (HHM). The humoral factor most commonly associated with HHM, including that of RCC, is parathyroid hormone-related protein (PTHrP) (Burtis et al. 1990; Mundy 1990). PTHrP causes hypercalcemia through bone resorption, as well as through renal calcium reabsorption (Rosol and Capen 1992). Partial sequence homology between PTHrP and parathyroid hormone (PTH) helps to explain the mechanisms by which this occurs. Unlike primary hyperparathyroidism, PTH levels are often normal or suppressed in cases of HHM (Walther et al. 1997; Flombaum 2000). Interleukin-6 (IL-6) and prostaglandin (PG), both of which stimulate osteoclast activity, represent additional humoral factors involved in HHM (Papac and Poo-Hwu 1999).

13.3.2

Presentation

The most common presenting symptoms of hypercalcemia are nonspecific and include fatigue, anorexia, nausea, and constipation. Through the induction of an osmotic diuresis and inhibition of antidiuretic hormone activity, hypercalcemia also causes polyuria and progressive dehydration. Not uncommonly, patients are found to have acute or chronic renal insufficiency at the time of presentation. Neurologic symptoms such as weakness, lethargy, and disorientation may progress into seizures, coma, and even death if treatment is delayed. Symptom severity depends upon the degree of hypercalcemia and the rate at which it develops.

13.3.3

Evaluation

Appropriate treatment of hypercalcemia depends upon the symptom severity, serum calcium level, renal function, and overall health status of the patient. Tumor stage and oncologic prognosis are also important and must be taken into consideration when formulating a management plan. Laboratory investigations include a CBC, serum electrolytes, ionized and total serum calcium, albumin, BUN, and serum creatinine. Serum magnesium should also be measured since hypercalcemia commonly induces renal magnesium wasting through actions exerted at the loop of Henle. Assays for PTHrP are available; however, the utility of this test is questionable at present. Perhaps in cases without a definitive diagnosis of malignancy, PTHrP and PTH levels should both be evaluated.

13.3.4

Treatment

Asymptomatic patients with mild to moderately elevated serum calcium (≤ 3.25 mmol/l, ≤ 14 mg/dl) do not require immediate treatment as an inpatient (Fojo 2005). Rather, medical therapy may be instituted on an outpatient basis with periodic monitoring of serum calcium and renal function. Symptomatic patients, or those with a serum calcium level above 3.25 mmol/l (> 14 mg/dl) indicating severe hypercalcemia require hospital admission and immediate intervention. The traditional and most basic treatment for hypercalcemia is i.v. hydration with isotonic saline. By increasing urine calcium excretion, hydration results in a rapid, yet modest (0.5 mmol/l) reduction in serum calcium levels. Renal function can also be expected to improve as the prerenal component of dysfunction is corrected. Hydration is generally begun with the infusion of 1–2 l of isotonic saline over 1–4 h (Flombaum 2000). Total volumes and rate of delivery will depend on the hydra-

Table 13.1. Treatment options for hypercalcemia of malignancy

Treatment	Dose	Route	Frequency
Normal saline hydration	1–2 l	IV	As necessary
Furosemide	20–40 mg	IV	As necessary
Zoledronate	4–8 mg over 5–15 min	IV	Every 4–6 weeks
Calcitonin	4–8 IU/kg	IM/SC	Every 6–8 h
Gallium nitrate	100–200 mg/ m ² /day × 5 days	IV	
Dialysis Nephrectomy			

tion and cardiovascular status of the patient. Furosemide, a loop diuretic that inhibits calcium reabsorption at the loop of Henle, can be used to augment renal calcium excretion. Loop diuretics should only be used when rehydration has been completed.

Rehydration alone is often inadequate (Hosking et al. 1981). The majority of patients with hypercalcemia of malignancy will require additional medical therapy as outlined in Table 13.1. The cornerstone of such therapy is the bisphosphonate group of medications. As pyrophosphate analogs with a high affinity for hydroxyapatite, bisphosphonates concentrate in areas of high bone turnover where they become internalized into osteoclasts and inhibit bone resorption (Fleisch 1991; Lin 1996; Sato et al. 1991; Fojo 2005). Three generations of bisphosphonates are now available, each providing an incremental improvement in potency, response duration, and toxicity profile. Etidronate, the original bisphosphonate, corrects hypercalcemia in 50% of patients; however, this is achieved at the expense of significant demineralization (Singer and Minoofar 1995). The success rate of second- and third-generation bisphosphonates exceeds 80% (Purohit et al. 1995; Nussbaum et al. 1993). The current drug of choice is zoledronate, a third-generation bisphosphonate that achieves normocalcemia in more than 90% of patients (Major et al. 2001). As with all bisphosphonates, this agent must be given intravenously because of poor oral absorption. Zoledronate usually corrects hypercalcemia within 4–10 days for a duration of 4–6 weeks. Bisphosphonates are more effective against hypercalcemia arising from focal bone destruction secondary to metastases than against HHM. Despite potent inhibition of focal and systemic bone resorption, bisphosphonates have no effect on renal calcium reabsorption, which plays a prominent role in HHM. Animal studies suggest that bisphosphonates may cause or exacerbate renal failure; therefore, these agents should be used with caution if the serum creatinine exceeds 3.0 mg/dl (Stewart 2005).

Calcitonin is another treatment option for hypercalcemia. Reduction in serum calcium occurs primarily

through the inhibition of osteoclast-mediated bone resorption. However, supraphysiologic doses have also been shown to improve renal calcium excretion (Lin 1996; Sato et al. 1991). Tachyphylaxis occurs within 2–3 days of repeated calcitonin dosing; therefore long-term efficacy is not possible. The primary utility of calcitonin lies in the rapidity of its onset (2–6 h) (Warrell et al. 1988). As such, calcitonin is ideally used in combination with longer-acting medications with delayed-onset such as bisphosphonates. With the exception of rare allergic reactions, calcitonin is considered safe and nontoxic.

Gallium nitrate, originally developed as an anticancer drug, is a potent inhibitor of bone resorption (Warrell et al. 1991). In addition to osteoclast inhibition, gallium nitrate reduces serum calcium through the inhibition of both renal calcium reabsorption and PTH secretion (Warrell et al. 1984; Warrell 1997). A continuous 5-day i.v. infusion corrects hypercalcemia in approximately 80% of patients for a median duration of 8 days (Warrell et al. 1991). Serum calcium begins to normalize within hours but maximal effect takes place after the infusion is complete. Ten percent of treated patients experience an elevation in serum creatinine; therefore, gallium nitrate should be used with caution in patients with baseline renal dysfunction (Zojer et al. 1999). Based on its lengthy administration protocol and potential for nephrotoxicity, gallium nitrate is rarely used today. It does, however, remain an important treatment option in cases of hypercalcemia refractory to bisphosphonate therapy.

Dialysis is indicated in patients with severe hypercalcemia complicated by significant mental changes. Patients with chronic renal failure or congestive heart failure often cannot tolerate i.v. hydration therapy; therefore, hemodialysis is frequently necessary in these cases as well.

Depending on the extent of disease and the oncologic prognosis, nephrectomy may also be a consideration. Hypercalcemia typically normalizes after nephrectomy in cases of localized RCC (Gold and Fefer 1996; Fahn et al. 1991). Persistence or relapse of hypercalcemia is often an indication of local recurrence or occult metastatic disease. Cytoreductive nephrectomy has been shown to correct hypercalcemia in two-thirds of patients with metastatic RCC; however, this effect is only temporary (Walther et al. 1997).

13.4 Complications of Bacille Calmette-Guérin Therapy

Bacille Calmette-Guérin (BCG) is the most effective intravesical agent available for the treatment of high-risk superficial transitional cell carcinoma (TCC) of the

bladder. A live attenuated strain of the bovine tuberculous mycobacterium, BCG exerts its antineoplastic effect through the stimulation of a nonspecific inflammatory reaction at the bladder level. Intravesical treatment is generally safe with fewer than 10% of patients experiencing complications that require treatment beyond symptomatic palliation (Lamm et al. 1992, Rischmann et al. 2000). Side effects can be categorized into local and systemic subtypes. The most common local toxicity is cystitis, with 80% of patients describing varying degrees of irritative voiding symptoms (Resel Folkersma et al. 1999). Low-grade fever (<38.5°C), which occurs in many as one-third of patients soon after intravesical therapy, is the most frequent systemic effect reported (Rischmann et al. 2000). The most serious toxic effects of BCG treatment include BCG-osis, manifested as pulmonary or hepatic infection, and BCG sepsis. Since both present with fever as an early sign, the difficulty lies in differentiating benign, transient fever from that which heralds serious systemic illness. Fortunately, BCG-osis and BCG sepsis each affect less than 1% of patients (Lamm et al. 1992).

In the setting of serious systemic illness following BCG therapy, suspicion for hematogenous dissemination of mycobacteria or other urinary tract pathogens should be high. Although BCG virulence and host immunocompetence play a role, trauma to the lower urinary tract is the most common predisposing factor (Lamm et al. 1992). This is reflected in the list of contraindications to intravesical BCG therapy, which include traumatic catheterization and gross or microscopic hematuria (Table 13.2) (Malkowicz 2002; Lamm et al. 1992). While the literature is sparse, small series have demonstrated no significant morbidity with the use of intravesical BCG in renal transplant patients (Palou et al. 2003). Apart from a lower rate of fever with the Pasteur strain, the relative rates of fever, BCG-osis and

Table 13.2. Contraindications to intravesical BCG therapy

Absolute	Relative
Traumatic catheterization	Microscopic hematuria
Gross hematuria	Poor performance status
Immunocompromised	Advanced age
Acquired immunodeficiency syndrome	Prior history of tuberculosis
Seropositive human immunodeficiency virus	
Leukemia	
Hodgkin's disease	
Transplant recipients	
Prior BCG sepsis	
Prior BCG-osis (pulmonary, hepatic)	
Intractable urinary tract infection	
Pregnancy	
Lactation	

BCG sepsis among the five commercially available strains of BCG are quite similar (Lamm et al. 1992). Prior febrile responses to BCG therapy and positive skin reactivity to purified protein derivative have both been shown to be predictive of an increased risk of fever and a trend toward an increased risk of systemic side effects (Lamm 1992; Bilen et al. 2003). Interestingly, patients who develop systemic side effects to BCG demonstrate longer disease-free and progression-free survival from an oncologic standpoint (Bilen et al. 2003; Suzuki et al. 2002). This implies that patients who mount an augmented systemic reaction toward BCG may also mount a more effective inflammatory response against the bladder tumor.

13.4.1

BCG-Related Fever

Low-grade fever (<38.5°C) in the absence of hemodynamic instability is a benign immune response to mycobacterial exposure in most cases. Outpatient symptomatic treatment with oral antipyretics is typically all that is necessary. Resolution should be expected within 24–48 h of treatment (Rischmann et al. 2000). High-grade fever (>39.5°C), which develops in 3%–4% of patients, or persistent low-grade fever are more worrisome (Lamm et al. 1992; Resel Folkersma et al. 1999). Current recommendations are to evaluate all patients with fevers above 38.5°C or 39.5°C lasting longer than 24 or 12 h, respectively, and to initiate single-agent antitubercular treatment on an empiric basis (Malkowicz 2002). The evaluation of BCG-related fever includes a CBC as well as serum electrolytes, creatinine, liver function studies, and mycobacterial blood cultures. Gram-negative sepsis is not an uncommon cause of fever in this patient population; therefore standard blood and urine cultures should also be obtained in order to rule out infection by common urinary pathogens. Respiratory symptoms suspicious for pulmonary infection warrant a plain radiograph of the chest. Isoniazid (INH) (300 mg once a day by mouth) is the antitubercular agent of choice for BCG-related fever. The most common adverse effect of INH is transient hepatitis manifest as elevated serum transaminase levels. This occurs in 10%–20% of patients and should normalize despite the continuation of treatment (Lamm et al. 1992). Isoniazid is continued for 3 months and need only be discontinued if transaminases rise above three times the upper limit of normal. Prophylactic INH has not been shown to reduce the incidence of fever or systemic infection (Durek et al. 2000). Moreover, prophylactic INH diminishes the immune response and impairs antitumor activity (de Boer et al. 1992).

13.4.2

BCG Sepsis

The most serious complication of BCG therapy is generalized sepsis secondary to intravascular absorption of mycobacteria or other urinary pathogens. Traumatic catheterization, identified in more than two-thirds of such cases, is the most common etiologic factor (Lamm 1992). Severe cystitis and recent transurethral surgery (within 1 week) are other potential routes for dissemination. Fever is the most common presenting sign and typically occurs within 12 h of BCG instillation (Paterson and Patel 1998). High-grade fever within 2 h of BCG instillation is especially worrisome, as is hemodynamic instability and other signs of multisystem organ failure (Dalbagni and O'Donnell 2006). Blood and urine cultures are typically negative. The mortality rate of BCG sepsis approaches 50%; therefore empiric triple-drug therapy is indicated in any patient with persistent fever and evidence of sepsis in temporal association with BCG administration (Malkowicz 2002; Paterson and Patel 1998). A 6-month course of INH, rifampin, and ethambutol is the current standard of care (Table 13.3). Ethambutol may be discontinued after 2 months depending upon organism susceptibility and clinical resolution (Blumberg et al. 2003). Since the treatment response to antitubercular medications is delayed by 2–7 days, traditional guidelines recommended concurrent therapy with cycloserine, an antibiotic capable of controlling mycobacteria within 24 h (Lamm et al. 1992; Lotte et al. 1984). Recent susceptibility studies, however, have demonstrated that commercially available BCG strains are highly resistant to cycloserine. In contrast, fluoroquinolones, gentamicin, and all antitubercular drugs, except pyrazinamide, retain activity against BCG (Durek et al. 2000). As such, contemporary guidelines recommend the addition of a fluoroquinolone or ampicillin plus gentamicin combination to standard antitubercular therapy in cases of BCG sepsis (Durek et al. 2000; Paterson and Patel 1998). This allows rapid inhibition of mycobacterial growth while also providing adequate empiric coverage for possible Gram-negative sepsis. The duration of treatment with supplementary antibiotics, determined by the results of

Table 13.3. Treatment of BCG sepsis

Medication	Dosage	Duration
Isoniazid plus	300 mg p.o. daily	6 Months
Rifampin plus	600 mg p.o. daily	6 Months
Ethambutol plus	1,200 mg p.o. daily	2–6 Months
Ampicillin plus	1 g i.v. every 6 h	Await culture results
Gentamicin ^a	7 mg/kg i.v. every 24 h	
Or ciprofloxacin	500 mg p.o. twice daily or 400 mg i.v. every 12 h	

^a Based on potential nephrotoxicity, gentamicin dosing requires assessment of renal function

standard blood and urine cultures, need only be short-term in true BCG sepsis. One caveat is the development of intolerance or systemic complication to any of the standard antitubercular drugs, in which case a fluoroquinolone may be used in substitution.

The use of corticosteroids in BCG sepsis is somewhat controversial. Severe type IV hypersensitivity is an important diagnosis to consider in any patient with suspected BCG sepsis. Since the two diagnoses are often difficult to differentiate, most authorities recommend the addition of corticosteroids (prednisolone 40 mg p.o. daily) or hydrocortisone 100 mg i.v. four times daily (Lamm 1992; Paterson and Patel 1998) to standard treatment in the short term. Animal studies have shown that prednisolone in combination with standard antitubercular therapy is more effective than standard therapy alone (DeHaven et al. 1992). Exacerbation of true BCG sepsis secondary to immunosuppression remains a concern; therefore the decision to continue steroid therapy should be made relatively soon, based on clinical and laboratory parameters.

13.4.3 BCG-osis

BCG-osis is a variant of systemic infection wherein the lungs, liver, or both are primarily affected (Malkowicz 2002). The clinical picture is similar to that of BCG sepsis; however, patients with BCG-osis are generally hemodynamically stable and present with signs and symptoms indicating pulmonary or hepatic disease. Although an abnormal chest radiograph or elevated liver enzymes suggest the diagnosis, only bronchoalveolar aspiration or biopsy of the lungs or liver are conclusive (Rischmann et al. 2000). Not uncommonly, these biopsies are negative, indicating that many such cases represent a hypersensitivity reaction rather than a true mycobacterial infection. Regardless, a 6-month course of INH and rifampin is indicated if clinical suspicion is high (refer to Table 13.3) (Lamm et al. 1992). Ethambutol is added if the patient is acutely ill, as are corticosteroids in cases unresponsive to standard treatment. A prior history of BCG sepsis or BCG-osis precludes future treatment with intravesical BCG.

13.5 Malignant Spinal Cord Compression

Spinal cord compression is a debilitating complication of metastatic cancer identified in 5%–14% of cancer patients (Patchell et al. 2005). Among urologic malignancies, it is most commonly seen with prostate cancer (PCa), which accounts for 9%–24% of cases overall (van der Linden et al. 2005; Flynn and Shipley 1991). In fact, PCa is the second most common cause of malig-

nant spinal cord compression, with a cumulative incidence of 7% (Manghani et al. 2000; Rosenthal et al. 1992; Sorenson et al. 1990). Although RCC and TCC account for 6% and 2% of cases, respectively, PCa, by virtue of its higher incidence and preponderance for vertebral metastases, warrants the bulk of discussion. However, despite a few minor variances, the treatment principles are the same regardless of malignant etiology.

Prostate cancer is the most commonly diagnosed noncutaneous malignancy in American men today and the second most common cause of cancer death (Jemal et al. 2005). Screening through the use of serum prostate-specific antigen (PSA) has led to both stage and risk migration such that the proportion of patients presenting with metastatic disease has fallen from 14.1% in 1988 to 3.3% in 1998 (Paquette et al. 2002). While distant metastatic disease is now uncommon at presentation, an additional 70% of patients with locally advanced PCa can be expected to develop metastases in follow-up (Coleman 1997). Skeletal metastases are the most common form of extralymphatic disease, and based on venous drainage patterns the bony pelvis and spine often represent the first sites involved.

In addition to significant pain and the potential for pathologic fracture, metastases to the vertebral column may cause spinal cord compression through local growth into the epidural space (Byrne 1992). Direct compression of the spinal cord causes edema, venous congestion, and demyelination, all of which impair neurologic function (Patchell et al. 2005). Prolonged compression eventually leads to infarction of the spinal cord. Without prompt diagnosis and treatment, progressive and irreversible loss of neurologic function will occur. All too often, however, presentation and diagnosis are delayed.

13.5.1 Presentation

Midline back pain is the most common presenting symptom (90%) (Gilbert et al. 1978; Sundaresan et al. 1985; Harrington 1988; Maranzano and Latini 1995). It is typically localized to the level of cord compression and, unlike degenerative disc disease, it is exacerbated by recumbency and improved by upright posture (Dodge et al. 1951). Radicular pain secondary to nerve root compression is less frequent but highly localizing. Symptom progression is usually slow with pain predating further neurologic changes by a median of 7 weeks (Quinn and DeAngelis 2000). Progression of neurologic dysfunction can, on occasion, take place over a matter of hours or days; therefore, new onset back pain in a cancer patient requires urgent evaluation.

Motor weakness is the second most common feature of cord compression. As a result of delays in both pre-

sentation and diagnosis, more than three-quarters of patients present with objective motor deficits (Gilbert et al. 1978; Harrington 1988). Regardless of the compression site, weakness begins in the legs and affects proximal muscle groups first (Quinn and DeAngelis 2000). Progression to paraplegia is typically a late event. Sensory changes are also common (50%) and occur soon after the onset of muscle weakness (Tazi et al. 2003). Symptoms include hyperesthesia at the level of compression or paresthesias and sensory loss in the toes with proximal ascent. Urinary retention, fecal incontinence, and impotence are usually late signs indicating autonomic dysfunction. An exception is cauda equina syndrome in which lumbar metastases cause compression of the conus medullaris. Autonomic dysfunction can occur early in this setting and sensory loss often assumes a saddle-like distribution.

13.5.2

Evaluation

Any cancer patient with new-onset back pain or neurologic change requires a thorough evaluation to rule out cord compression. A meticulous neurologic exam is performed to determine the initial spinal level and severity of compression. Interval changes are documented through periodic repeat examinations. A normal neurologic exam does not exclude the presence of impending cord compression. Up to 36% of patients with back pain and no neurologic deficits will have epidural metastases demonstrated on imaging (Rodichok et al. 1981). MRI is the imaging modality of choice in cases of suspected spinal cord compression (Fig. 13.3) (Manglani et al. 2000; Quinn and DeAngelis 2000). While plain radiography allows a quick assessment of vertebral collapse and deformity, MRI provides an accurate determination of both the degree of compression and the number of cord levels affected. A total of 10%–38% of cases involve multiple noncontiguous levels; therefore, the entire spine must be imaged (Byrne 1992; Helweg-Larsen et al. 1995). The thoracic spine is the most common site of cord compression, and accounts for approximately two-thirds of cases involving PCa (Flynn and Shipley 1991). CT with or without myelography may be used in cases where MRI is contraindicated or unavailable. Serum PSA and testosterone levels should be measured in cases of PCa to determine the androgen sensitivity of the malignancy.

13.5.3

Treatment

As a late manifestation of advanced disease, the treatment of malignant spinal cord compression is palliative. The primary objectives are pain relief and neurologic preservation while reduction of tumor bulk re-



Fig. 13.3. Spinal cord compression. MRI demonstrating neoplastic replacement of L3 and L4 vertebrae and epidural compression of spinal cord in patient with metastatic prostate cancer

mains a secondary goal only. Available treatment options include medical, radiation, and surgical therapies, which are typically delivered in a multidisciplinary fashion. Historically, intravenous corticosteroids in combination with external beam radiotherapy (EBRT) were the treatment of choice. Recent advances in spinal instrumentation and surgical techniques have led to a renewed interest in the use of surgery as primary therapy. Since there are no large-scale studies of urologic or PCa-related spinal cord compression, current guidelines are based upon the results of studies incorporating numerous tumor types. Although oncologic prognosis, presence of co-morbidities, and overall performance status are important, ambulatory status and spinal stability at presentation are the primary considerations when formulating a treatment plan. Numerous studies have demonstrated the prognostic significance of baseline ambulatory status with regard to treatment outcome. The majority of ambulatory patients can expect to remain ambulatory with early treatment, whereas only 50% of nonambulatory patients, at best, can expect the same (Ok et al. 2005).

Table 13.4. Steroid protocols for malignant spinal cord compression

Dexamethasone	Bolus	Maintenance
High dose	100 mg i.v.	24 mg i.v./p.o. every 6 hs for 3 days then taper
Moderate dose	10 mg i.v.	4 mg p.o./i.v. every 6 h for 3 days then taper

Regardless of ambulatory status and spinal stability, corticosteroids are the first treatment administered in cases of suspected or confirmed spinal cord compression. Through a rapid reduction in vasogenic edema, corticosteroids decrease mechanical compression on the spinal cord until more definitive therapy can be provided. Additional steroid actions include pain relief, reduction in inflammation, and a direct oncolytic effect (Ok et al. 2005). Corticosteroids can be given in both high-dose and moderate-dose schedules (Table 13.4) (Manghani et al. 2000). The two dosing schedules appear to provide similar rates of neurologic and ambulatory preservation; however, high-dose corticosteroids are associated with superior analgesia at the expense of a greater risk of steroid-related complications (gastrointestinal ulceration, psychosis, *Pneumocystis carinii* pneumonia) (Heimdal et al. 1992; Delattre et al. 1988). Since no randomized controlled trials have directly compared these two schedules, it is difficult to make firm recommendations for steroid dosing. To minimize the potential for steroid-related morbidity, it has been suggested that corticosteroid therapy begin with the moderate dose schedule. If neurologic improvement does not occur within 6–12 h, the high-dose schedule can be implemented at that time (Manghani et al. 2000). Maintenance dosing is continued until the neurologic status remains stable for 48 h, after which steroids are tapered over 2–3 weeks.

Androgen deprivation therapy maintains an important role in the treatment of metastatic spinal cord compression involving hormonally naïve PCa. Unfortunately, most patients with PCa who develop spinal cord compression have exhausted hormonal therapy and are resistant to such therapy. Nevertheless, all PCa patients require an evaluation of serum PSA and testosterone to determine the level of androgen sensitivity that remains. Hormonally naïve cases demonstrate improved ambulatory rates (80% vs 42%) and overall survival (16 vs 6 months) relative to hormone-resistant cases when androgen deprivation is incorporated into the overall management plan (Iacovou et al. 1985; Flynn and Shipley 1991). Methods available for hormonal therapy include both surgical (bilateral orchiectomy) and chemical (ketoconazole) castration. Orchiectomy and ketoconazole allow the most immediate reduction in serum testosterone levels. Ketoconazole, an oral synthetic imidazole antifungal agent, reduces

gonadal and adrenal testosterone synthesis through the inhibition of cytochrome P450 enzyme-dependent 14-demethylation of lanosterol to cholesterol. At a dose of 400 mg three times daily, ketoconazole suppresses serum testosterone to castrate levels within 48 h (Trachtenberg 1984). Prostate cancer-related spinal cord compression with neurologic compromise is a relative contraindication to the use of luteinizing hormone-releasing hormone (LHRH) agonists. These agents induce a temporary rise in serum testosterone, termed the flare phenomenon, which begins within 2–3 days and lasts approximately 1 week from the initiation of therapy (Bubley 2001). Such a rise in serum testosterone may lead to symptomatic disease progression, which, in the context of documented spinal cord compression, can involve a further deterioration in neurologic function. Patients in whom spinal cord compression is impending rather than proven may be candidates for LHRH agonist therapy; however, pretreatment with a steroidal or nonsteroidal antiandrogen is recommended. Antiandrogen therapy is preferably begun 1 week before the initiation of LHRH agonist treatment and continued for 1 month. Luteinizing hormone-releasing hormone antagonists, such as abarelix, represent an acceptable alternative to LHRH agonists since they rapidly achieve castrate serum testosterone levels (68%–78% within 7 days, 96% within 1 month) and avoid the testosterone surge altogether (Trachtenberg et al. 2002; Koch et al. 2003). Abarelix has demonstrated safe and effective provision of medical castration in men with symptomatic PCa, including those with impending spinal cord compression (Koch et al. 2003).

Ambulatory patients with spinal stability are usually managed nonoperatively. For this group, the gold standard treatment is corticosteroids in combination with EBRT. Radiotherapy is begun soon after the initiation of corticosteroids with dosages of 2,000–4,000 cGy administered over a 2- to 4-week period (Manghani et al. 2000). For optimal results, the radiation portal includes a margin of one or two vertebral bodies above and below the site of compression (Quinn and DeAngelis 2000). Radiotherapy decreases cord compression through a reduction in tumor mass and bone turgor. Paradoxically, this may lead to weakening of the vertebral body and subsequent collapse; therefore, patients often require 6–10 weeks of external bracing while bone healing takes place. Preservation of ambulation can be expected in 70%–100% of patients treated in this manner (Sundaresan et al. 1985; Maranzano and Latini 1995; Katagiri et al. 1998; Helweg-Larsen 1996; Tomita et al. 1983). Radiotherapy and corticosteroids together are more effective than EBRT alone with ambulatory rates of 81% and 61%, respectively, demonstrated in a randomized controlled trial (Sundaresan et al. 1985).

Nonambulatory, nonparaplegic patients with stable spines are more difficult to manage. Significant motor

deficit is a sign of severe and longstanding spinal cord compression and only a minority of treated patients can be expected to regain the ability to walk. Corticosteroids plus EBRT provide post-treatment ambulatory rates of 6%–60% and likely favor the lower end of this spectrum (Maranzano and Latini 1995; Tomita et al. 1983; Turner et al. 1993; Sorensen et al. 1994; Leviov et al. 1993). Based on a clear inferiority to EBRT and a lack of proven benefit in combination with EBRT, surgery has not had a prominent role in this subgroup. However, this practice was based upon the results of decompressive laminectomy, a historical procedure with inferior outcomes. Although most vertebral metastases are located anterior to the spinal cord, laminectomy typically removes only posterior elements and does not remove the bulk of the compressive tumor. Furthermore, laminectomy may actually destabilize the spine, thereby worsening postoperative ambulatory rates. Over the past two decades, vertebrectomy and spinal stabilization have gained popularity based on the successful results of several nonrandomized studies (Siegel et al. 1982, 1985; Harrington 1984; Sundaresan et al. 1984; Overby and Rothman 1985; Klimo et al. 2005). This procedure, which takes an anterior approach, seeks to decompress the spinal cord through the resection of all gross disease. Concurrent spinal instrumentation provides immediate spinal stabilization even in cases of near-total vertebral body excision.

A recent randomized trial comparing vertebrectomy plus spinal stabilization in combination with EBRT vs EBRT alone has confirmed the utility of primary surgery in cases of metastatic spinal cord compression (Patchell et al. 2005). Postoperative ambulatory rates (84% vs 57% overall) and duration of ambulation (median, 122 days vs 13 days) were both superior with direct decompressive surgery, regardless of baseline ambulatory status. In fact, 62% of nonambulatory patients regained the ability to walk after surgery compared to 19% with radiation alone. Although this study did not include patients with paraplegia persisting longer than 48 h, older series suggest that immediate surgery is also advantageous in this group (Barcena et al. 1984). Unfortunately, only a minority of paraplegic patients (<30%) can expect to regain ambulation with such treatment. The superior functional results of surgery likely reflect the provision of immediate decompression before irreversible spinal infarction takes place as well as the removal of maximal tumor bulk, which minimizes the possibility of malignant regrowth and secondary compression. Of importance, no excess morbidity or mortality could be ascribed to surgery and the mean duration of hospitalization was only 10 days in both groups. Although this randomized study demonstrated a superior functional outcome with surgery for both ambulatory and nonambulatory patients, vertebrectomy and spinal stabilization is not yet considered

Table 13.5. Indications for surgical management of spinal cord compression secondary to prostate cancer metastases

Surgical indications

Spinal instability or vertebral body collapse
 Nonambulatory patients who fail to respond to radiotherapy
 Progressive neurologic deterioration during radiotherapy
 Bone extending into spinal canal causing thecal compression
 Radiculopathy with progressive or uncontrolled symptoms
 Spinal cord compression in a previously irradiated area
 Paraplegic or severely paraparetic patients with recent neurologic deterioration

a panacea. Commonly accepted indications for surgical decompression are outlined in Table 13.5 (Baehring 2005).

13.6 Neutropenia

Neutropenia, defined as an absolute neutrophil count of less than 500 cells/ μ l, occurs frequently in cancer patients undergoing systemic chemotherapy. Among patients with genitourinary malignancies, this scenario is most common in patients with advanced TCC of the bladder. In this setting, the administration of MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) or GC (gemcitabine, cisplatin) chemotherapy leads to the development of grade 3 or 4 neutropenia (World Health Organization classification) in 80% and 43%–71% of patients, respectively (von der Masse et al. 2000). Although less frequent, neutropenia may also occur with conventional (bleomycin, etoposide, cisplatin) and salvage (ifosfamide-based) chemotherapy during the treatment of metastatic germ cell cancer (Bosl et al. 2005).

Neutrophils represent the first cellular component of the inflammatory response. As such, neutropenia poses significant risk for the development of infection. Both the degree and duration of neutropenia have been shown to correlate strongly with the incidence of serious infection (Bodey et al. 1966). Numerous risk factors have been identified for the development of neutropenia and subsequent infection. Patient-specific risk factors include hematologic malignancy, advanced tumor stage, significant co-morbidities, poor performance status, and advanced age, while treatment-specific risk factors include chemotherapy type and dose intensity (Crawford et al. 2004). Incorporation of these risk factors into predictive models serves to guide prophylaxis and treatment recommendations against neutropenia (Lyman et al. 2005).

The inflammatory response to infection is severely weakened in the setting of neutropenia. Not only does this predispose to the development and rapid progression of infection, but it also lessens the associated signs and symptoms thereof. To prevent the development of

infection and infection-related complications, it is essential that neutropenic cancer patients receive prompt evaluation and appropriate management. Antimicrobial prophylaxis for the prevention of infection is controversial. While clinicians are divided on its use, current guidelines recommend against the use of prophylactic antibiotics in neutropenic patients without fever, citing a lack of consistent reduction in mortality rates as well as concern over the emergence and propagation of drug-resistant bacteria and fungi (Hughes et al. 2002). An exception to this rule is found in patients considered to be at high risk for the development of *Pneumocystis carinii* pneumonitis. In these patients, prophylactic trimethoprim-sulfamethoxazole is recommended. Hematopoietic growth factors such as granulocyte colony-stimulating factor (filgrastim) or granulocyte-macrophage colony-stimulating factor (sargramostim) represent additional potential treatment options. When given as primary prophylaxis, these agents can reduce the incidence of febrile neutropenia by as much as 50% (Ozer et al. 2000). However, the American Society of Clinical Oncology (ASCO) does not recommend the routine use of prophylactic colony-stimulating factors in patients undergoing chemotherapy since no improvements in survival or response rate have been demonstrated with such practice (Ozer et al. 2000). Likewise, therapeutic colony-stimulating factor is not recommended as routine treatment for afebrile neutropenic patients based on a demonstrated lack of clinical benefit. Finally, adjustments to the chemotherapy regimen may become necessary in some neutropenic patients. Although this allows for bone marrow recovery, it should be considered an option of last resort since lower cancer-specific survival is well documented among patients receiving less than full-dose chemotherapy (Lepage et al. 1993; Budman et al. 1998).

13.6.1

Febrile Neutropenia

Febrile neutropenia is defined as: (1) a single oral temperature above 38.3°C or a temperature of 38.0°C or higher lasting longer than 1 h, and (2) an absolute neutrophil count below 500 cells/μl (Hughes et al. 2002). Of bladder cancer patients undergoing CMV or MVAC chemotherapy regimens, 10%–14% meet these established criteria (Gilligan et al. 2003). The importance of febrile neutropenia lies in the fact that infection is the most common cause of fever in the neutropenic setting (50%) and, in turn, the leading cause of chemotherapy-related death (Schimpff 1986). As such, fever in the context of neutropenia is considered to reflect active infection until proven otherwise.

13.6.1.1 Evaluation

Patients that meet the criteria for febrile neutropenia require urgent evaluation. The purpose of initial evaluation is twofold: (1) assess for the presence and site of infection and (2) determine the risk of significant infection-related complications. Evaluation begins with a thorough history and meticulous physical examination. Among immunocompromised patients, the classic signs and symptoms of infection are unreliable. A complete head-to-toe examination should be undertaken wherein every minor finding suspicious as a site or route of infection is investigated further. The gastrointestinal tract, lungs, skin, mouth, and pharynx deserve special consideration since endogenous flora originating from these sites account for the majority of neutropenic infections (Marchetti and Calandra 2004; Crawford et al. 2004). Careful evaluation of surgical scars, biopsy sites and venous catheter sites, if present, should also be made. The perineum and perianal region are often overlooked sites of infection that require careful inspection and palpation.

The initial laboratory evaluation includes a CBC and differential, electrolytes, BUN, creatinine, liver function studies, as well as cultures of blood (two sites) and urine. Sputum, cerebral spinal fluid, skin lesions, and stool should also be cultured if there is clinical suspicion of infection involving these sites. Most recommend obtaining a plain chest radiograph in all patients regardless of clinical findings. Ambulatory patients without clinical signs of pulmonary infection do not routinely require imaging of the chest because it is often of low diagnostic yield (Oude Nijhuis 2003; Sipsas et al. 2005). Laboratory and radiologic examinations may be insensitive markers of infection in the setting of neutropenia. As an example, up to 89% of febrile neutropenic patients with urinary tract infection lack pyuria and 40% of patients with pneumonia will have no abnormal findings on chest radiography.

13.6.1.2 Treatment

Empiric antibiotic therapy forms the cornerstone of treatment for febrile neutropenia and should be started immediately upon diagnosis. With such treatment, reductions in infection-related mortality have been observed over the past three decades. However, a mortality rate of 8% among contemporary hospitalized cancer patients with febrile neutropenia would seem to indicate that this condition remains a serious threat to life (Crawford et al. 2004). It has become clear that patients with febrile neutropenia are not all alike, and treatment regimens may be individualized. The Infectious Diseases Society of America (IDSA) has published guide-

Table 13.6. Infectious Diseases Society of America (IDSA) recommended antibiotic regimens for empiric treatment of febrile neutropenia

Setting	Regimen
Low risk	Ciprofloxacin plus amoxicillin-clavulanate
High risk	
Monotherapy	Cefepime or Ceftazidime or Imipenem or Meropenem
Combination	Aminoglycoside plus Antipseudomonal penicillin or Cephalosporin (cefepime or ceftazidime) or Carbapenem
Combination with vancomycin	Cefepime or ceftazidime ± aminoglycoside or Carbapenem ± aminoglycoside or Antipseudomonal penicillin + aminoglycoside

lines to facilitate the treatment of cancer patients with neutropenic fever (Table 13.6) (Hughes et al. 2002). A complete review of this complex topic is beyond the scope of this chapter; however, the treatment principles deserve discussion.

The IDSA treatment guidelines are based upon an individualized assessment of risk as determined by prognostic models. One such model, the Multinational Association of Supportive Care in Cancer (MASCC) Scoring Index, accurately predicts the risk of infection-related complications in neutropenic patients based upon seven clinical variables each with independent prognostic significance (Klastersky et al. 2000) (Table 13.7). Patients are generally divided into two groups: (1) low-risk (<5% risk of developing serious infection-related complications) and (2) high-risk (all other patients). Low-risk, compliant patients may be treated on an outpatient basis with oral antibiotics, the preferred agents being ciprofloxacin in combination with amoxicillin-clavulanate. In contrast, high-risk patients require hospitalization for i.v. antibiotics and close monitoring. The antibiotic of choice in high-risk patients is controversial and depends upon patient, cancer, and pathogen-related factors. Gram-negative bacilli and Gram-positive cocci are the predominant organisms involved and account for one-third and two-thirds of all cases, respectively (Table 13.8) (Hughes et al. 2002). Not only should the selected antibiotic regimen provide broad coverage of both groups, but it should also reflect the prevalence and susceptibility profiles of the individual institution. Historically, all patients received aminoglycoside-containing combination antibiotic therapy. The results of numerous contemporary studies have found that empiric antibiotic monotherapy provides similar efficacy to combination therapy in cases of uncomplicated neutropenic fever,

Table 13.7. The Multinational Association of Supportive Care in Cancer (MASCC) Risk Scoring Index for identification of low-risk febrile neutropenic patients at presentation

Characteristic	Score ^a
Extent of illness ^b	
No symptoms	5
Mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no fungal infection	4
No dehydration	3
Outpatient at onset of fever	3
Age < 60 years ^c	2

^a Highest theoretical score is 26. A risk index score of ≥ 21 indicates that the patient is likely to be at low risk for complications and morbidity

^b Choose one item only

^c Does not apply to patients ≤ 16 years of age

Table 13.8. Most common bacterial causes of febrile neutropenia

Gram-positive cocci	Gram-negative bacilli
Staphylococcus species	<i>Escherichia coli</i>
Coagulase-positive (<i>S. aureus</i>)	<i>Klebsiella</i> species
Coagulase-negative (<i>S. epidermidis</i> and others)	<i>Pseudomonas aeruginosa</i>
Streptococcus species	
<i>S. pneumoniae</i>	
<i>S. pyogenes</i>	
Viridans group	
<i>Enterococcus faecalis</i> , <i>E. faecium</i>	
<i>Corynebacterium</i> species	

but with a lower rate of adverse reactions (De Pauw et al. 1994; Furno et al. 2002). This has led to a paradigm shift in treatment such that empiric antibiotic monotherapy is now considered appropriate for the majority of patients. The IDSA currently recommends four antibiotics as appropriate empiric monotherapy: ceftazidime, cefepime, imipenem, and meropenem (Hughes et al. 2002). Piperacillin-tazobactam represents a fifth monotherapy option with proven efficacy (Bow et al. 2003). Combination antibiotic therapy remains the standard of care for low-risk cases treated with oral therapy, high-risk cases involving hemodynamic instability, and cases arising from institutions with a high-frequency of multidrug-resistant pathogens. Recommended combination regimens include an aminoglycoside with an antipseudomonal β -lactam or cephalosporin (Table 13.6). The decision to add vancomycin is based upon a presumed risk of Gram-positive infection rather than routine practice. Indications for its empiric use include (1) apparent catheter-related infection; (2) positive blood culture for a Gram-positive bacterium; (3) colonization with methicillin-resistant *Staphylococcus aureus*; and (4) hemodynamic instability without an identifiable organism (Segal et al. 2005).

The response to treatment is evaluated after 2–3 days of therapy. If the causative organism is identified, antibiotics may be tailored accordingly. Unfortunately, the causative organism is confirmed in only one-third of patients (Bodey et al. 1978). In the event that the culture results are inconclusive, low-risk patients who remain afebrile and clinically stable may be switched to, or continued on, oral ciprofloxacin plus amoxicillin-clavulanate. Patients who demonstrate persistent fever after 3–5 days of empiric therapy are at risk for cryptic foci (e.g., abscess, endocarditis), resistant organisms, as well as fungal or viral infections (Sipsas et al. 2005). These patients require repeat evaluation and, most likely, modification of empiric antibiotic therapy. This should be done in consultation with an infectious disease specialist knowledgeable in the care of cancer patients. The recommended duration of antibiotic therapy for febrile neutropenia depends upon the absolute neutrophil count, presence or absence of fever on day 3, culture results, clinical course, and overall risk strata. The reader is referred to the 2002 IDSA guidelines in this regard (Hughes et al. 2002).

Antifungal therapy deserves appropriate consideration in cases of persistent neutropenic fever. Fungal infections account for 2%–10% of neutropenic infections overall, and up to 30% of infections in patients with persistent neutropenic fever (Wisplinghoff et al. 2003; de Pauw et al. 1994). Furthermore, fungal septicemia carries with it a high mortality rate, which approaches 90% in certain subgroups of patients (Sipsas et al. 2005). Based on the high prevalence and significant mortality of fungal infections, the IDSA recommends the empiric initiation of systemic antifungal therapy in neutropenic patients with fever persisting 5 days despite appropriate empiric antibiotic therapy (Hughes et al. 2002). *Candida* and *Aspergillus* species constitute the most common fungi identified. The drug of choice is amphotericin B, although fluconazole is an acceptable alternative. In contrast, there is no indication for empiric antiviral therapy in febrile neutropenic patients, nor are colony-stimulating factors routinely recommended. The use of antiviral agents is generally limited to cases of documented viral respiratory tract infection or documented herpes simplex or varicella-zoster cutaneous infection. Cutaneous viral infections, even if not the source of fever, require treatment since they are potential portals of entry for bacteria and fungi. Acyclovir, valacyclovir, or famciclovir are all appropriate antiviral treatment options.

13.7 Intractable Bladder Hemorrhage

Gross hematuria is not uncommon among patients with genitourinary malignancies. It can be the presenting sign of cancer involving the urinary tract or it may

arise as a direct complication of cancer treatment. In most cases, the hematuria is of mild to moderate severity and resolves with conservative measures. Some cases, however, involve intractable hemorrhage that can be life-threatening without prompt and effective treatment. Intractable gross hematuria usually arises from the bladder secondary to advanced urothelial carcinoma, severe infection, chemotherapy-induced hemorrhagic cystitis, and radiation cystitis. Not only are these disease processes the most common causes of severe bladder hemorrhage, but they are also among the most difficult to treat. The optimal management of intractable bladder hemorrhage rests upon a determination of its cause and the institution of specific treatment at that time. Commonalities do exist, however, and they form the basis for management guidelines with broad application to all patients with severe bladder hemorrhage.

13.7.1 Transitional Cell Carcinoma

Transitional cell carcinoma (TCC) of the bladder is the fourth and ninth most common cancer in men and women, respectively (Jemal et al. 2005). Gross or microscopic hematuria is the typical manner of presentation (>80%). Seventy-five percent of patients are found to have superficial TCC while the remaining 25% are diagnosed with muscle-invasive disease. Treatment is primarily surgical with transurethral resection and radical cystectomy representing the standard options for superficial and invasive TCC, respectively. Since hematuria arises from the tumor itself, isolated or recurrent episodes of bleeding can be expected to resolve upon resection of the primary tumor. Exceptions do exist, however. These include: (1) large or locally advanced tumors deemed unresectable by cystectomy and (2) invasive tumors diagnosed in patients whose health status precludes cystectomy. Transurethral resection alone is inadequate in these cases and patients often develop troublesome hematuria as a consequence of inevitable tumor progression. Patients with advanced bladder cancer who fail conservative measures, as outlined below, may receive benefit from the addition of external beam radiotherapy. Radiotherapy for this purpose is generally well tolerated and may lead to resolution of hematuria in up to 59% of patients (Srinivasan et al. 1994).

13.7.2 Hemorrhagic Cystitis

Hemorrhagic cystitis is defined as gross hematuria secondary to diffuse inflammation of the bladder. Viral infection, radiation-induced inflammation, and chemotherapy-induced inflammation account for the majority of cases among cancer patients. While relatively un-

common in patients with genitourinary malignancies, viral-mediated hemorrhagic cystitis occurs in as many as 50% of patients undergoing bone marrow transplantation (Bedi et al. 1995). The principle etiologic factor involved is the BK polyomavirus. Viral-mediated hemorrhagic cystitis often occurs several weeks after transplantation and is usually self-limited. The role of antiviral therapy is unclear at present; therefore, no specific treatment recommendations beyond standard hematuria management can be made for viral hemorrhagic cystitis.

The association between hemorrhagic cystitis and the oxazaphosphorine alkylating agents, cyclophosphamide and ifosfamide, has been well documented (Philips et al. 1961; Burkert 1983; Klastersky 2003). These chemotherapeutic drugs are used frequently in the treatment of breast cancer, lymphoma, and sarcoma but also have application in poor-risk and chemotherapy-resistant germ cell tumors. Cyclophosphamide is associated with a 24% incidence of irritative voiding symptoms, 7%–53% incidence of microscopic hematuria, and 1%–15% incidence of gross hematuria (Talar-Williams et al. 1996). Older series report hemorrhagic cystitis in as many as 68% of patients treated with cyclophosphamide (Burkert 1983). The causative agent of urothelial toxicity is acrolein, a hepatic metabolite eliminated primarily through urinary excretion (Cox 1979). Peak urine levels occur approximately 5 h after the start of chemotherapy infusion (Takamoto et al. 2004). Early pathologic changes include transmural edema, mucosal ulceration, and urothelial necrosis all of which may occur within 24 h of a single dose (DeVries and Freiha 1990). With repeated exposure, urothelial damage is progressive and may become irreversible (Forni et al. 1964; Koss 1967). The entire urothelium is at risk; however, the bladder is most frequently affected as it receives the longest exposure. In the acute setting, cystoscopy reveals diffuse inflammatory changes, while in the delayed setting chronic changes such as edema, pale mucosa, telangiectasia, and patchy inflammation are prominent (Coleman and Walther 2005).

Contemporary studies report a lower incidence of hemorrhagic cystitis secondary to cyclophosphamide than do historical series. This is due in large part to the development and routine application of preventative measures such as hydration and prophylactic mesna (sodium 2-mercaptoethane sulfonate). Intravenous normal saline is given concurrently with cyclophosphamide infusion to reduce the urinary concentration of acrolein through an increase in urine output (Philips et al. 1961). Unfortunately, the prevention of clinically significant urothelial damage is inconsistent with hydration; therefore, hydration therapy alone cannot be recommended as adequate prophylaxis. Mesna, a non-toxic thiol compound, was specifically developed to bind and inactivate acrolein without interfering with

tumor control (Brock et al. 1981). Numerous randomized trials have demonstrated the superiority of mesna relative to placebo and hydration in the prevention of gross hematuria (Araujo and Tessler 1983; Fukuoka et al. 1991; Shepherd et al. 1991). With the routine incorporation of mesna into cyclophosphamide or ifosfamide-containing chemotherapy regimens, modern rates of severe hematuria range from 0%–13%. Mesna must be administered before cyclophosphamide to ensure adequate urinary levels are available when acrolein reaches peak urinary concentration. For this reason, mesna has no place in the treatment of established cyclophosphamide-induced hemorrhagic cystitis. Based on simplicity, convenience, and proven efficacy, a two-dose mesna regimen (15 min before and 4 h after cyclophosphamide) is recommended (Katz et al. 1995). There is suggestion that the addition of dexamethasone may improve the prophylactic efficacy of mesna (Vieira et al. 2003). Prior episodes of hemorrhagic cystitis do not absolutely contraindicate the repeat administration of cyclophosphamide or ifosfamide provided that mesna is given prophylactically (Andriole et al. 1987).

The management of cyclophosphamide-induced hemorrhagic cystitis can be difficult. At the present time, there is no specific therapeutic option that can be recommended ahead of standard management strategies. Intravesical prostaglandin (PGE₁, PGE₂, and PGF₂α) therapy is one option that may hold future promise. Initial interest in the use of prostaglandins was generated by case reports of demonstrated success in cases of otherwise intractable bladder hemorrhage secondary to cyclophosphamide (Miller et al. 1994; Trigg et al. 1990; Shurafa et al. 1987). Subsequent series report 50% complete resolution of hematuria after the administration of carboprost tromethamine (PGF₂α) for a median treatment period of 6 days (Levine and Jarrard 1993). Although the exact mechanism of action is unknown, prostaglandin may improve hematuria through platelet aggregation and vasoconstriction. Bladder spasms (78%) are a frequent occurrence with intravesical prostaglandin therapy; however, adverse effects on renal or bladder function are negligible as are systemic complications. Prostaglandins have since found application in the management of other forms of severe hemorrhagic cystitis. Hyperbaric oxygen treatment (HBO), typically reserved for cases of refractory radiation cystitis, has also been used to treat hemorrhagic cystitis resulting from cyclophosphamide. Animal models suggest that HBO may be of value as prophylaxis or treatment in this setting (Hader et al. 1993).

13.7.3

Radiation Cystitis

Radiation cystitis is a late complication of radiotherapy which, by definition, occurs at least 90 days after the

initiation of radiation treatment but may be delayed up to 10 years or more (Cox et al. 1995). Most patients develop severe irritative voiding symptoms; however, gross hematuria dominates the clinical picture (Pasquier et al. 2004). While any patient receiving pelvic radiotherapy is at risk, radiation cystitis is most common among those treated for prostate or cervical cancer. Three to five percent of such patients will develop late grade 3 hematuria, the incidence of which is directly related to both the biologic dose and the volume of tissue irradiated (Perez 1998; Lawton et al. 1991; Shipley et al. 1988; Dearnaley et al. 1999). In contrast to acute changes, late radiation injuries are irreversible and often progressive. There appears to be no correlation between the development of early and late radiation injuries. The pathophysiology of late radiation damage includes cellular depletion, fibrosis, and obliterative endarteritis (Pasquier et al. 2004). All of these changes lead to tissue ischemia and, in turn, delayed wound healing. Cystoscopically, such changes give the appearance of pale, frosted mucosa, scattered telangiectasia, and ulcers (Rigaud et al. 2004).

Radiation cystitis is perhaps the most difficult form of bladder hemorrhage to treat. The reason for this lies primarily in the ischemic nature of the injury and the propensity toward poor wound healing. Based on a lack of randomized controlled trials comparing available treatment options, firm guidelines for radiation cystitis management cannot be made (Denton et al. 2002). That being said, a tremendous amount of research has been devoted to examining the role of hyperbaric oxygen therapy (HBO) in the treatment of radiation injuries. First introduced into the field of radiation oncology in 1953 as a radiosensitizer, HBO has subsequently been shown to ameliorate radiation damage among a wide range of tissues, including the bladder (Gray et al. 1953; Capelli-Schellpfeffer and Gerber 1999; Feldmeier and Hampson 2002). Hyperbaric oxygen therapy involves the inhalation of 100% oxygen pressurized to 1.4–3.0 atm in sessions of 60–120 min. Under these conditions, alveolar, arterial, and tissue oxygen levels are driven to supraphysiologic levels. By improving the oxygenation of irradiated tissue, HBO stimulates angiogenesis, fibroblast proliferation, and collagen formation (Marx et al. 1990). Not only does this promote wound healing, but the vasoconstriction induced by an abundance of oxygen may also help to control bleeding (Capelli-Schellpfeffer and Gerber 1999). Retrospective studies examining the role of HBO in severe radiation cystitis report response rates of 77%–100% (complete response, 34%–100%; partial response, 12%–45%) (Mathews et al. 1999; Neheman et al. 2005). A single prospective study of HBO demonstrated an overall response rate of 92.5% among 40 patients with radiation cystitis refractory to standard measures (Beverly et al. 1995). Patients underwent 20 treatment sessions inhaling

100% oxygen at 3 atm for 90 min each. With a mean follow-up of 23 months, the recurrence rate of severe hematuria was 12% per year. It is difficult to predict the individual treatment outcome; however, the provision of HBO within 6 months of hematuria onset appears to improve the response rate (96% vs 66%, $p=0.003$) (Chong et al. 2005). Cancer patients who do not respond to HBO require evaluation for cancer recurrence since this is a common cause of persistent hematuria (Rijkmans et al. 1989). Hyperbaric oxygen therapy is generally well tolerated, with adverse events limited to case reports of visual disturbance, spontaneous pneumothorax, oxygen toxicity seizures, hypoglycemia, and loss of respiratory drive in hypercapnic patients (Capelli-Schellpfeffer and Gerber 1999). Contraindications to the use of HBO are listed in Table 13.9 (O'Reilly et al. 2002). Concern exists over the theoretic risk of cancer stimulation through HBO-mediated neoangiogenesis, immune suppression, and free radical toxicity. A review of the world literature in 2003, however, found that available *in vitro*, *in vivo*, and clinical studies suggested no more than a neutral effect of HBO on tumor growth (Feldmeier et al. 2003). Additional studies have found no evidence that exposure to hyperbaric oxygen promotes tumor growth, including that of prostate cancer (Chong et al. 2004). As such, a history of malignancy should not be considered a contraindication to treatment with HBO. Perhaps the largest obstacle to its use is cost. The average cost per session is \$ 300–\$ 400, which amounts to an estimated \$ 10,000–\$ 15,000 per patient (Norkool et al. 1993). While there exist no formal cost-comparisons among available treatments for radiation cystitis, HBO is still regarded as a cost-effective option and should be considered for refractory cases.

WF10, the *i.v.* formulation of a novel wound-healing agent, tetrachlorodecaoxygen, has demonstrated benefit in patients with wound healing disorders, including that arising from radiation injury (Hinz et al. 1986; Veerasarn et al. 2004). As an immune modifier, WF10 promotes the healing process through the inhibition of the chronic inflammatory process. Two human studies, including one randomized trial have evaluated the efficacy

Table 13.9. Contraindications to use of hyperbaric oxygen therapy

Absolute contraindications	Relative contraindications
Untreated pneumothorax	Upper respiratory infections
Concurrent treatment with	Seizure disorders
Cis-platinum	High fevers
Doxorubicin	History of spontaneous pneumothorax
Bleomycin	Viral infections
Disulfiram	Congenital spherocytosis
Mafenide acetate	History of optic neuritis
	History of otosclerosis

cy of this novel agent in the treatment of radiation cystitis (Veerasarn et al. 2004, 2006). Among cervical cancer patients with grade 2 or 3 radiation cystitis, WF10 provided a complete response rate of 74%–88%. Although this was not statistically superior to the standard hematuria measures employed in the control arm, patients treated with WF10 demonstrated a lower rate of hematuria recurrence (47% vs 77%, $p=0.01$) and a longer estimated time to recurrence (>300 days vs <100 days, $p=0.004$). The administration protocols in both studies involved 0.5 mg/kg WF10 in 250 ml normal saline infused over 2 h on 5 consecutive days every 3 weeks for two cycles. Transient hemoglobinemia may occur in up to one-quarter of treated patients; however, there have been no serious safety concerns with WF10 in these or any other studies to date. At this time, the role of WF10 in the management of radiation cystitis remains investigational.

13.7.4

Treatment of Intractable Bladder Hemorrhage

The approach to the patient with intractable bladder hemorrhage is fairly standard and begins with a thorough evaluation to determine its cause. Information obtained on history (e.g., prior malignancy, prior radiotherapy, prior cyclophosphamide, etc.) may suggest the etiology; however, multiple factors may be involved and assumptions should not be made. Outside of the acute setting, all cases in which the etiology has not been identified require a formal hematuria workup, including cystoscopy, urine cytology, and upper tract imaging. The chronicity and severity of the hematuria as well as any prior attempts at therapy are important to determine. This may suggest to what degree, if any, the hematuria is refractory to conservative measures. Patients with severe hematuria can develop urinary retention secondary to the accumulation of blood clot within the bladder; therefore, the ability to void should be questioned. A list of the patient's current medications should be reviewed and any anticoagulants discontinued accordingly. The primary goals of physical examination are to determine the hemodynamic stability and overall health status of the patient as well as the presence of urinary retention. Laboratory studies should include a CBC and differential, serum electrolytes, BUN, creatinine, coagulation profile, and urine culture. Initial therapy is directed toward maintaining hemodynamic support through i.v. fluids as well as through blood and blood product replacement as necessary.

Whatever the etiology, the management of gross hematuria follows the same general principles as outlined in Table 13.10. Treatment is delivered in a stepwise manner according to hemodynamic stability, hematuria severity, and treatment response. A hematuria

Table 13.10. Graded management options for intractable bladder hemorrhage

Clot evacuation (catheter or cystoscopic) plus
Intermittent saline irrigation or
Continuous saline irrigation
Cystoscopy ± fulguration
Oral agents
E-aminocaproic acid (Amicar) (loading 5 g p.o./i.v., then maintenance 1 g/h) ^a
Sodium pentosan polysulphate (Elmiron) (begin 100 mg p.o. three times daily)
Intravesical agents
Alum 1% (250 ml/h via continuous bladder irrigation) ^b
Prostaglandin-E1, -E2, and -F2 α (see text for dosing)
Formalin (begin $\leq 4\%$, up to 10%)
Hyperbaric oxygen therapy
Embolization of internal iliac artery
Surgery (urinary diversion, with or without open bladder packing or cystectomy)

^a Maximum daily dose of Amicar is 30 g

^b Do not exceed 3 g/h alum in patients with renal insufficiency

Table 13.11. Hematuria grading system and suggested management

Grade	Treatment
Mild	
No acute decrease in hematocrit (Hct)	Saline irrigation Oral Amicar or Elmiron Intravesical alum
Moderate	
Drop in Hct	Above plus
Requires ≤ 6 HU of packed red blood cells to maintain hemodynamic stability	Clot evacuation Cystoscopy ± fulguration Intravesical prostaglandin or formalin
Urinary clot retention	
Severe	
Refractory to saline irrigation, Amicar, alum, prostaglandin	Above plus: Intravesical formalin Embolization
Requires >6 HU of packed red blood cells to maintain hemodynamic stability	Surgery

grading system has been proposed to facilitate treatment in this regard (Table 13.11) (DeVries and Freiha 1990). The first step involves bladder decompression through the insertion of a large-bore urethral catheter for clot evacuation and saline lavage. This is a simple maneuver that may slow or stop the bleeding altogether. Continuous bladder irrigation (CBI) through a three-way Foley catheter is initiated once the effluent is clear or pink-tinged and free of clots. In some instances, bedside lavage is inadequate and formal cystoscopic clot evacuation in the operating room becomes necessary. During this time, the bladder is carefully inspected for a source of hemorrhage, and biopsies or fulguration of suspicious areas can be performed. Cases not responsive to clot evacuation and fulguration or those with cystoscopic evidence of diffuse hemorrhage

require supplementary therapy with systemic or intravesical agents.

E-aminocaproic acid (Amicar), given orally or parenterally, inhibits the process of fibrinolysis by preventing the activation of plasminogen to plasmin. It is used commonly in the field of cardiothoracic surgery based on demonstrated efficacy in the reduction of postoperative hemorrhage (Trinh-Duc et al. 1992). Unfortunately, there have been no comparative trials evaluating the efficacy of this agent in the context of hemorrhagic cystitis. Proponents of its use for bladder hemorrhage cite anecdotal reports of apparent success in addition to the evidence provided by disciplines outside of urology (Aroney et al. 1980; Lakhani et al. 1999; Stefanini et al. 1990). Administration involves a loading dose of 5 g followed by 1 g/h for 8 h or until bleeding stops. The maximum recommended dosage in 24 h is 30 g. As an inhibitor of fibrinolysis, E-aminocaproic acid promotes clot formation; therefore, it should be used in conjunction with CBI. Upper tract hemorrhage remains a contraindication to its use since clot formation within the ureter can lead to obstruction and acute renal failure.

Sodium pentosan polysulphate (Elmiron), given orally, is a low-molecular-weight heparinoid that replaces deficient glycosaminoglycans on the bladder surface (Parsons et al. 2002). In doing so, it removes potential triggers of hematuria by protecting the bladder wall from bacterial adherence as well as from the absorption of toxic substances within the urine. Such protection may also facilitate healing of the bladder surface. While used more commonly in the treatment of interstitial cystitis, sodium pentosan polysulphate has been shown to resolve hematuria in 50% of patients with radiation or cyclophosphamide-induced hemorrhagic cystitis when given as first-line treatment (Parsons et al. 1993; Sandhu et al. 2004). Dosing begins at 100 mg three times daily with a gradual reduction to 100 mg daily as hematuria improves. Treatment may be discontinued when the hematuria resolves completely. At this time, there is no data available regarding the rate or time to recurrence with such therapy.

Of the commonly used intravesical agents, alum and prostaglandins have the advantage of not requiring an anesthetic. Alum (aluminium ammonium sulphate or aluminium potassium sulphate) is an astringent that causes protein precipitation, vasoconstriction, and decreased capillary permeability without damaging normal urothelium (Ostroff and Chenault 1982; Arrizabala et al. 1987). Commonly delivered as a 1% solution (50 g alum in 5 l sterile water) via CBI at a rate of 250 ml/h, alum leads to the complete resolution of hematuria in 60%–100% of hemorrhagic cystitis patients (Ostroff and Chenault 1982; Gattegno et al. 1990; Choong et al. 2000). The median time to resolution of hematuria ranges from 3–4 days, but therapy may be required for as long as 7 days. Up to 20% of patients will

develop recurrent hematuria within 5–10 months. The risk of systemic toxicity is low because urothelial permeability to aluminum is minimal and prompt renal excretion ensures elevated aluminum levels are avoided. There are case reports of aluminum encephalopathy with intravesical alum, the majority of which occurred in patients with baseline renal insufficiency (Kavoussi et al. 1986; Shoskes et al. 1992; Perazella et al. 1993). In addition to central nervous system disturbance (lethargy, confusion, seizures), aluminum toxicity can result in metabolic acidosis and coagulopathy. While renal failure is not an absolute contraindication to the use of intravesical alum, it should be used with caution and at a dose that should not exceed 3 g/h (Kennedy et al. 1984). Aluminum levels should be monitored periodically in such patients. Intravesical alum irrigation should be discontinued immediately if serum aluminum levels are elevated or systemic toxicity is suspected.

Prostaglandin-E₁, -E₂, and -F₂ α , already discussed as a treatment option for cyclophosphamide-induced hemorrhagic cystitis, may prove beneficial in cases arising from a variety of other causes as well. Numerous protocols for prostaglandin administration have been described including: (1) 50 ml of 4–10 mg/l of carboprost tromethamine left indwelling for 2 h four times per day alternating with saline CBI and (2) 8–10 mg/l of PGF₂ α via saline CBI at a rate of 100 ml/h for 10 h (Choong et al. 2000). Both protocols lead to a complete response in 50% of patients treated over a median period of 6 days (Levine and Jarrard 1993). A small trial comparing intravesical PGF₂ α and 1% alum in patients with hemorrhagic cystitis of unknown origin demonstrated similar response rates of 80% and 90%, respectively (Praveen et al. 1992). Although there was a complete lack of systemic side effects in both groups, virtually all patients developed transient bladder spasms requiring symptomatic control. Since prostaglandins are very expensive, 1% alum remains the intravesical agent of first choice.

The best known and most effective intravesical hemostatic agent is formalin, the aqueous solution of formaldehyde. When administered intravesically, formalin rapidly fixes the bladder mucosa through a process involving protein cross-linking. This prevents further necrosis and blood loss from occurring (DeVries and Freiha 1990). First introduced in 1969 for the treatment of radiation cystitis, 10% formalin led to the complete resolution of hematuria in 22 of 24 patients with no serious side effects noted (Brown 1969). Since that time, formalin has also demonstrated success in the treatment of hemorrhagic cystitis. At the same time, the potential for serious toxicity (up to 15%) with bladder formalinization is well documented. In light of the potential for significant treatment-related morbidity, formal instillation is generally reserved for cases of in-

tractable bladder hemorrhage refractory to conservative treatment.

The results of a meta-analysis evaluating 235 cases of intractable bladder hemorrhage treated with intravesical formalin form the foundation upon which most recommendations are made (Donahue and Frank 1989). Formalin can be administered intravesically in concentrations ranging from 1%–10% (typically 1%, 5%, 10%). While there is a trend toward improved results with 10% formalin, there is no statistical difference in complete response among the three preparations (71%–83%). Hematuria typically resolves within 48 h (1–5 days) and the duration of response is 3–4 months, regardless of dose. Major complications (5%–15%) include bladder contracture, ureteral stenosis, acute renal failure, and even death. Although there appears to be a trend toward a higher rate of major complications with higher concentrations of formalin, this has never been proven. Similarly, the rate of minor complications (14%–78%), of which irritative voiding symptoms are most common, appear to correlate with dose. Given the lack of comparative studies it is difficult to make firm recommendations regarding the optimal concentration of formalin. There is some suggestion that hematuria secondary to radiation cystitis may require 5% or more formalin, while hematuria due to cyclophosphamide or bladder cancer may require less than 5% formalin; however, this is merely conjecture. Most centers advocate the initial use of 4% or less formalin since this concentration appears to optimize the treatment response (>75%) while minimizing the potential for minor and major complications (Russo 2000).

Formalin must be instilled under a spinal or general anesthetic since it is caustic to the sensory nerves of the bladder. The procedure begins with a formal cystoscopic evaluation of the entire bladder and urethra. Clot evacuation and fulguration of bleeding vessels can be performed as necessary. Vesicoureteric reflux significantly predisposes the patient to upper tract damage with intravesical formalin; therefore a cystogram must be performed prior to every instillation. Documented reflux is not a contraindication to formalin treatment but does necessitate the insertion of occlusive Fogarty balloon catheters into the affected ureteric orifice(s) (Gottesman and Ehrlich 1974). Reverse Trendelenburg positioning and the induction of a brisk diuresis can also protect against the reflux of formalin. The presence of bladder perforation, which remains an absolute contraindication to the use of formalin, can also be documented by a cystogram. Prior to beginning formalin instillation, the entire perineum should be painted with petroleum jelly and, in women, the vagina packed with petroleum jelly gauze to protect exposed skin and mucosa from the caustic effect of formalin. Through an 18-F Foley catheter, the bladder is then filled to capacity with 1%–2% formalin under gravity at a pressure kept below 15 cm H₂O

(catheter level at 15 cm above pubic symphysis). Although the optimal contact time is not known, most recommend limiting the treatment session to 15 min (Choong et al. 2000).

Approximately 10%–30% of patients with severe hemorrhagic cystitis will not respond to low-dose formalin instillation. A second instillation using high-dose formalin (5%–10%) remains an option; unfortunately, repeat administration of formalin is associated with a lower complete response rate (50%) and a higher rate of major complications (40%). Treatment alternatives include hyperbaric oxygen therapy, arteriographic embolization, and urinary diversion with or without cystectomy. Hyperbaric oxygen is most appropriate for refractory radiation cystitis as described above; however, animal studies suggest that it may also be of benefit in cases of cyclophosphamide-induced hemorrhagic cystitis (Hader et al. 1993).

Therapeutic embolization of the internal iliac artery to control bladder hemorrhage was first reported in 1974 (Hald and Mygind 1974). Most studies report a response rate in excess of 80%, usually of immediate onset (McIvor et al. 1982; Rodriguez et al. 2003; Nabi et al. 2003). A common complication of embolization is severe transient gluteal pain caused by claudication of the superior gluteal artery (Choong et al. 2000). Case reports of leg ischemia and bladder necrosis also exist (Woodside et al. 1976; Braf and Koontz 1977). Improvements in both technology and technique have led to superselective embolization. With such procedures, the efficacy of embolization is maintained while patient morbidity is reduced (De Berardinis et al. 2005). Embolization is most appropriate for those patients who are refractory to conservative measures, including formalin instillation, but whose health status precludes surgical intervention.

Open surgery is an option of last resort to be used only in patients with massive intractable bladder hemorrhage who are otherwise good surgical candidates. Open cystotomy combined with bladder packing and percutaneous urinary diversion, cutaneous ureterostomy, and cystectomy with urinary diversion have all been described, each with variable outcome (Andriole et al. 1990; Pomer et al. 1983; Okaneya et al. 1993). Unfortunately, many patients with severe hemorrhagic cystitis are elderly and unfit for invasive surgery. It is in situations such as this that intractable bladder hemorrhage becomes a lethal event.

13.8 Ureteral Obstruction

Malignant ureteral obstruction is not rare among cancer patients, with a cumulative incidence of 4.4% in advanced cases (Coleman and Walther 2005). While pel-

vic genitourinary malignancies such as ovarian, cervical, bladder, and prostate cancer (PCa) are the most common causes of malignant ureteral obstruction (70%), retroperitoneal lymphadenopathy secondary to lymphoma, and germ cell cancer are not uncommon (Holden et al. 1979). Obstruction may result from intramural tumor growth, extramural compression, or from retroperitoneal fibrosis secondary to cancer treatment (Montana and Fowler 1989). Approximately 2.5% of women who undergo definitive radiation treatment for cervical cancer will develop ureteral obstruction (McIntyre et al. 1995).

13.8.1

Presentation

The manner of presentation of ureteral obstruction depends upon the time course over which it develops and whether or not both sides are involved. Acute unilateral obstruction presents with the symptoms typical of renal colic while chronic unilateral obstruction tends to be clinically silent and is most often identified through the incidental detection of hydronephrosis on abdominal imaging. Bilateral obstruction, acute or chronic, presents with decreased urine output and signs and symptoms of uremia.

13.8.2

Evaluation

Evaluation of the patient with suspected ureteral obstruction begins with a complete history and physical examination. Laboratory evaluation includes a CBC,

serum electrolytes, BUN, creatinine, and urine culture. Since patients with ureteral obstruction may require the placement of percutaneous nephrostomy tubes, coagulation parameters should be routinely measured if obstruction is suspected. It is of the utmost importance to rule out the presence of concomitant urinary tract infection. Fever and flank pain together with leukocytosis and pyuria suggest urosepsis, a urologic emergency. Without prompt endoscopic or percutaneous decompression, obstructed uropoiesis is a potentially lethal condition. Upper tract imaging should be performed in all cases of suspected ureteral obstruction. Available options include intravenous pyelography, retrograde pyelography, antegrade pyelography, renal ultrasonography, radionuclide renography, and CT or MRI of the abdomen and pelvis (Fig. 13.4). These studies can confirm the presence and site of obstruction and may also provide clues as to the etiology. In this regard, CT and MRI provide the best anatomic detail of the retroperitoneum and pelvis (Fig. 13.5). Upper tract imaging can also establish the presence and severity of obstructive uropathy. The finding of small atrophic kidneys with marked cortical thinning indicates chronic obstruction (Fig. 13.6). Renal deterioration secondary to chronic obstruction is unlikely to improve with decompression; therefore, intervention is reserved for infected renal units (Logothetis et al. 2003).

13.8.3

Treatment

The management of malignant ureteral obstruction is controversial and depends upon many factors includ-

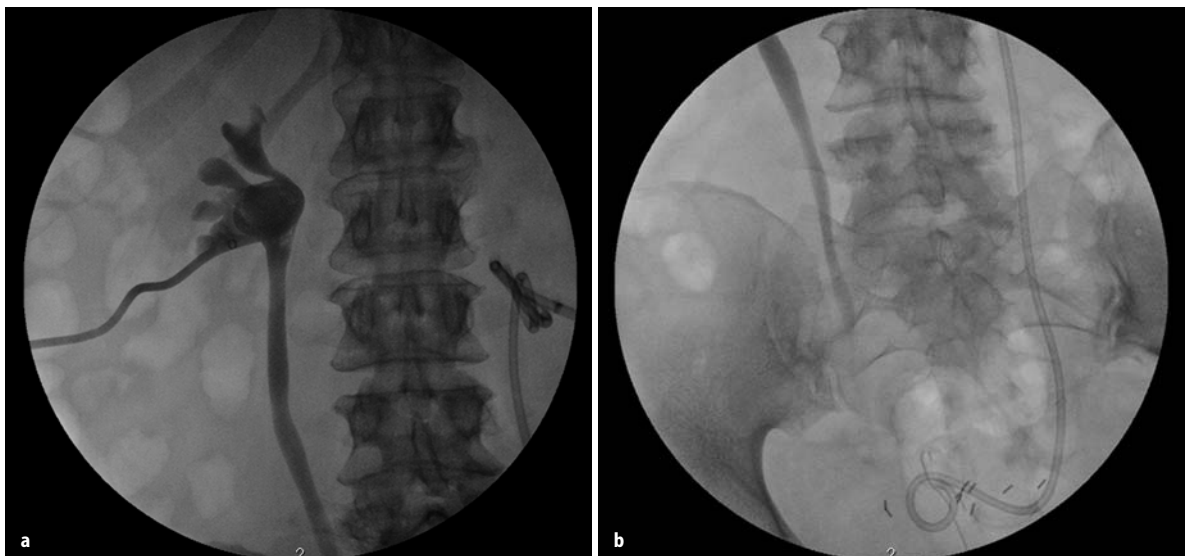


Fig. 13.4a–c. Distal ureteric obstruction in patient with locally recurrent cervical cancer. **a** Antegrade nephrostogram demonstrating left hydronephrosis and hydroureter, indwelling ureteric stent is visualized within right ureter. **b** Obstruction visualized at level of distal right ureter, no contrast within bladder.



Fig. 13.4c. Ureteric stent placed beyond point of obstruction



Fig. 13.6. Atrophic left kidney. Noncontrast CT demonstrating left hydronephrosis and renal atrophy in patient with distal ureteric obstruction

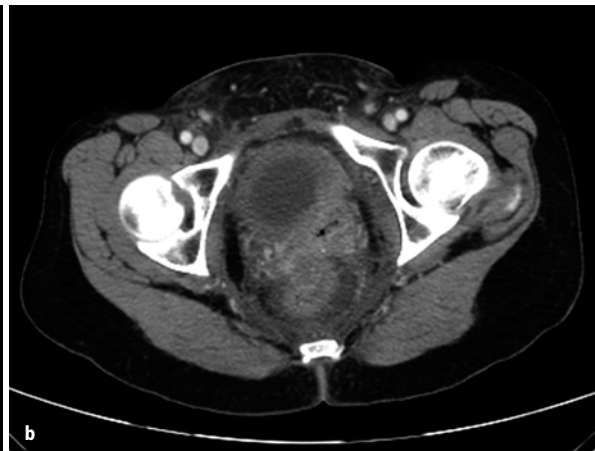


Fig. 13.5a, b. Distal ureteric obstruction in patient with locally recurrent cervical cancer. **a** CT demonstrating bilateral hydronephrosis. **b** Posterior pelvic mass invading and displacing posterior bladder wall

ing oncologic prognosis, quality of life, and treatment-related complications. Quite often, malignant ureteral obstruction is a late presentation of advanced, incurable malignancy and portends a poor prognosis. In this circumstance, the provision of ureteral decompression is unlikely to improve either the quality or quantity of life. The median survival of patients with active malignancy who undergo renal decompression through internal or external drainage is only 3–7 months (Wilson et al. 2005; Donat and Russo 1996; Shekarriz et al. 1999). The only situation in which ureteral decompression is uniformly recommended is in the infrequent circumstance that an improvement in renal function will facilitate the provision of therapeutic or palliative chemotherapy (Russo 2000). Lymphoma and germ cell cancer represent two such chemotherapy-sensitive malignancies wherein maximal preservation of renal

function is an important determinant of chemotherapy delivery and ultimate success (Logothetis et al. 2003; Ondrus et al. 2001).

Noninvasive treatment modalities, including retrograde internal ureteral stent (IUS) insertion and radiology-guided percutaneous nephrostomy (PCN) insertion, are most appropriate for malignant ureteral obstruction. It is difficult to make a firm recommendation in either regard since the quality of life they afford appears to be similar and both options have an equally high complication rate (13%–63%) (Little et al. 2003; Ganatra and Loughlin 2005; Donat and Russo 1996; Shekarriz et al. 1999). Stent or PCN-related infection, obstruction, migration, and dislodgement are common and often necessitate prolonged hospitalization. In experienced hands, PCN drainage can be established in 98% of cases, with a major complication rate of 4% (re-

nal hemorrhage requiring transfusion, vascular injury, sepsis, bowel injury, lung injury) and a mortality rate of 0.05%–0.3% (Dyer et al. 1997; Stables 1982). Cystoscopic IUS insertion appears to have a higher initial failure rate (15%–79%) than PCN, leading some authors to propose that PCN should be the management option of first choice in the acute setting (Ganatra and Loughlin 2005; Chitale et al. 2002; Park et al. 2002). Likewise, the accumulated incidence of recurrent obstruction may be higher with IUS (11%) than with PCN (1.3%) (Ku et al. 2004). Numerous studies have sought to determine if tumor type, degree of hydronephrosis, and level of obstruction are predictive of treatment failure; however, the results have thus far been contradictory (Ganatra and Loughlin 2005). That being said, some centers do recommend immediate PCN for ureteral obstruction secondary to advanced cervical cancer citing high failure rates with IUS in the short and long term (Ku et al. 2004). Cystoscopic evidence of tumor invasion appears to predict for IUS failure; therefore, radiographic imaging suspicious for involvement of the bladder and ureteral orifice is an indication for initial PCN. One-third of patients will ultimately fail IUS within 6 months and require long-term PCN due to repeat obstruction. Attempts to improve the long-term success rates of IUS include frequent stent exchange (every 3 months) and the ipsilateral insertion of two indwelling ureteral stents (two 7-F stents) (Ganatra and Loughlin 2005; Rotariu et al. 2001). Periodic imaging to confirm interval resolution or improvement of hydronephrosis is also warranted in patients with IUS. Despite the relatively high failure rate of IUS, most authorities recommend a trial of retrograde ureteral stents in all patients without obvious involvement of the distal ureter and bladder (Ganatra and Loughlin 2005). Likewise, PCN tubes should be converted to IUS in an antegrade fashion after a period of renal decompression. Situations in which retrograde stent insertion is advisable over PCN include those in which anatomic anomalies present a technical challenge to PCN insertion (e.g., horseshoe kidney) or cases involving a solitary kidney in which renal loss secondary to PCN-related renal hemorrhage would be disastrous (Uthappa and Cowan 2005).

Decompression of solitary or bilaterally obstructed kidneys may result in a postobstructive diuresis with urine output in excess of 200 ml/h. Most commonly, this reflects the appropriate excretion of excess sodium, urea, and water retained during the period of obstruction. Apart from the provision of oral fluids and the periodic evaluation of serum electrolytes, this form of diuresis requires no specific intervention. Serum creatinine and blood urea nitrogen typically normalize within 48 h. On occasion, a pathologic diuresis involving water or sodium-wasting may ensue secondary to significant distal renal tubular damage. Vital statistics in-

cluding postural blood pressure measurements should be performed on a frequent basis if a pathologic diuresis is suspected. These patients require careful monitoring and copious fluid replacement with 0.9% or 0.45% saline in order to avoid dehydration and electrolyte abnormalities.

In light of the significant long-term complication rate associated with mechanical drainage, patients with IUS or PCN require periodic monitoring with serum creatinine, urine culture, and upper tract imaging. Ureteral stents and percutaneous nephrostomy tubes should be exchanged every 3–4 months to prevent encrustation and obstruction. Depending on the chemotherapy or radiation-sensitivity of the etiologic malignancy, mechanical drainage may not be required indefinitely. Most cases of extrinsic obstruction secondary to germ cell or lymphomatous retroperitoneal lymphadenopathy will resolve with appropriate cytotoxic chemotherapy (Logothetis et al. 2003). Likewise, up to 70% and 85% of patients with hormonally naïve locally advanced PCa treated with androgen ablation or radiotherapy, respectively, will experience a relief of obstruction, obviating the need for mechanical drainage (Michigan and Catalonia 1977; Megalli et al. 1974).

Malignant ureteral obstruction is, in most cases, a manifestation of advanced, incurable disease and portends a poor prognosis. Even with the establishment of mechanical internal or external drainage, the median survival is 3–6 months among the most common etiologic malignancies. Furthermore, treatment-related morbidity is high and patients can expect to spend a significant portion of their remaining days in hospital (18%–46%) (Little et al. 2003; Romero et al. 2005). While IUS or PCN appear to be of questionable benefit in the palliative setting, they retain utility in the treatment of chemotherapy or radiation-sensitive malignancies. Clearly, this is a situation in which treatment, however minimally invasive it may be, should be approached in a cautious manner and only after due consideration has been given to the ultimate prognosis as well as the wishes of a fully informed patient and family.

13.9

Bladder Outlet Obstruction

Acute urinary retention is not uncommon in cancer patients, particularly those with genitourinary malignancies. Numerous etiologies exist and can be grouped into two broad categories: (1) mechanical bladder outlet obstruction (BOO) and (2) neurophysiologic dysfunction. Localized growth of PCa is a common cause of BOO. While symptomatic presentation is uncommon today, up to 82% of patients with PCa in the pre-PSA era presented with symptoms of urinary obstruction (Brawn et al. 1994). Furthermore, up to 35% of PCa pa-

tients placed on watchful waiting will eventually require transurethral prostatectomy (TURP) for symptomatic progression or urinary retention (Whitmore et al. 1991). Likewise, surgical and nonsurgical therapies directed toward prostate cancer may predispose to urinary retention. Bladder neck contracture (BNC) is reported in 1.3%–27% of patients after radical prostatectomy and 1.5%–22% of patients will develop urinary retention following prostatic brachytherapy (Anger et al. 2005; Stone and Stock 2002).

Neurophysiologic bladder dysfunction may arise secondary to medication side effects, postoperative pain and immobility, radical pelvic surgery, and chronic disease such as diabetes mellitus. Preexisting bladder dysfunction is common among elderly patients and even minor insults can trigger urinary retention. Medications with anticholinergic, sympathomimetic, and opioid activity are well known for their adverse effects on bladder function in this regard and should be discontinued or substituted if possible. Up to 50% of patients undergoing abdominoperineal resection or radical hysterectomy will develop bladder dysfunction as a result of interruption of parasympathetic innervation (Eickenberg et al. 1976). Fortunately, urinary retention secondary to radical pelvic surgery will spontaneously resolve in up to 90% of patients thus affected.

13.9.1 Evaluation

The diagnosis of urinary retention is established relatively easily. Patients typically complain of severe suprapubic pain and the inability to void. Physical examination often reveals a lower midline abdominal mass; however, dullness with percussion of the lower abdomen may be a more sensitive sign of bladder fullness. Apart from establishing urinary drainage, the next step is to differentiate mechanical obstruction from neurophysiologic dysfunction. Pelvic and rectal examination may identify a large obstructing pelvic tumor, while a focused neurologic exam demonstrating sensory or motor abnormalities may suggest a neurophysiologic cause. Further enquiry should be made into baseline voiding status, prior episodes of retention and associated treatment, overall health status, as well as the presence of medications or chronic illnesses known to undermine bladder function. Since urinary tract infection can complicate or precipitate urinary retention, the presence of irritating voiding symptoms or fever should be questioned. Renal insufficiency may complicate longstanding or severe urinary retention; therefore, azotemia and associated electrolyte abnormalities must be ruled out. Laboratory evaluation includes a CBC, serum electrolytes, BUN, and serum creatinine. Once urine becomes available, a urinalysis and urine culture should also be performed. Imaging of the upper

tracts is indicated if renal dysfunction is present. Renal size and cortical thickness may suggest the degree and duration of obstruction and may also provide some measure of salvageable renal function. Ultrasound appears to be the most cost-effective imaging modality in this regard (Reisman et al. 1991).

13.9.2 Treatment

The first step in the management of urinary retention, regardless of etiology, is bladder decompression through the insertion of a urethral Foley catheter. Should this prove difficult, attempts should be made to insert a coude-tipped catheter. Difficult catheterization often indicates the presence of an obstructing process such as urethral stricture or prostatic in-growth, benign or malignant. Situations such as this may require formal cystoscopy and possible urethral dilation for catheter insertion. In the event that all attempts at catheterization fail, the insertion of a suprapubic cystostomy tube is the most appropriate alternative. This can usually be performed percutaneously at the bedside. A history of lower abdominal or pelvic surgery is a contraindication to the percutaneous insertion of an suprapubic tube since intervening bowel may be injured. In this circumstance, suprapubic drainage should be established under radiologic guidance or in the operating room through open techniques.

Relief of longstanding bladder outlet obstruction can result in a postobstructive diuresis. This most commonly reflects the appropriate excretion of retained sodium, water and urea; however, a concentrating defect or a sodium-wasting nephropathy, both secondary to distal renal tubular damage, may also play a role. Management is similar to that arising from upper tract obstruction.

Once bladder decompression has been achieved, further management is dictated by the underlying pathologic process. Depending on the patient's health and prior voiding status, a trial of voiding is warranted in most cases. Retention secondary to neurophysiologic bladder dysfunction often resolves after a period of bladder decompression. Cases in which spontaneous voiding is slow to return require the initiation of clean intermittent catheterization every 4–6 h (Lapides et al. 1972). Intermittent catheterization has demonstrated clear superiority over chronic indwelling catheterization in terms of preserving upper tract function and minimizing urinary tract infection and stone formation. Benign prostatic hypertrophy alone or together with neurologic dysfunction warrants a trial of α -adrenergic blockade (Flomax 0.4 mg p.o. daily) and/or 5- α -reductase inhibition (Finasteride 5 mg p.o. daily) therapy.

Locally advanced prostate cancer, not uncommonly, precipitates urinary retention through compression of

the prostatic urethra and bladder neck. The most appropriate initial therapy in the hormonally naïve patient is androgen deprivation therapy. This may involve either surgical (bilateral orchiectomy) or chemical castration (LHRH agonist). Although castrate levels of serum testosterone are achieved much more rapidly with bilateral orchiectomy (immediate) than with LHRH agonist therapy (3–4 weeks), the reduction in prostate and tumor volume is delayed with both, as is the ability to spontaneously void. Two-thirds of patients thus treated will ultimately regain the ability to void; however, roughly 50% of patients will require catheterization for a period of 21–60 days in the interim (Fleischmann and Catalona 1985). Temporary drainage can be achieved through either continuous or intermittent catheterization, depending on the ease of catheterization. Up to 22% of patients will develop urinary retention a mean of 21 months after the initiation of hormonal therapy (Sehgal et al. 2005). Prognostic factors for urinary retention in this circumstance include a high Gleason score (>7) and urinary retention at the start of hormonal therapy. Those cases that are unresponsive to androgen deprivation or known to be resistant at baseline require TURP or intraprostatic urethral stenting. The insertion of a urethral stent is most appropriate for those patients who are poor surgical candidates and refuse an indwelling catheter. As many as 88%–100% of patients are able to void through a urethral stent with acceptable morbidity out to 1 year (Ok et al. 2005; Guazzoni et al. 1994). Based on concerns over the risk of infection and possible obstruction secondary to progressive tumor growth, urethral stents are only recommended in patients with a limited life expectancy.

Palliative or channel TURP is the gold standard treatment for PCa-related urinary retention unresponsive to medical therapy. Although less successful and associated with more complications than TURP performed for BPH, palliative TURP is considered a safe and efficacious procedure. Up to 79% of patients will regain the ability to void despite the relatively high rate of failure at initial trial of voiding (42%) (Crain et al. 2004). Morbidity is acceptable with an 8% transfusion rate and negligible perioperative mortality rate. The reoperation rate is relatively high (22%–29%) and likely reflects less than complete resection (mean 12-g resection), continued local tumor growth, and the propensity of tumor to bleed (Mazur and Thompson 1991; Crain et al. 2004). Photoselective vaporization of the prostate (PVP) using high-power potassium-titanyl-phosphate (KTP) laser energy is a relatively new procedure that appears to be an acceptable alternative to standard TURP for symptomatic obstructive uropathy secondary to either PCa or BPH (Sulser et al. 2004). Although no randomized controlled trials have compared these two modalities in the setting of PCa, similar improvement in peak flow rates and urinary symptom scores

have been demonstrated in patients with BPH (Shingleton et al. 1999). Perceived advantages to PVP include less bleeding, lower transfusion rate, shorter catheterization, and more rapid convalescence (Kumar 2005).

Chronic catheterization via an indwelling urethral or suprapubic catheter is an option of last resort typically reserved for terminally ill patients or those who fail medical and surgical therapies. Suprapubic catheterization may be preferable to urethral catheterization based on long-term data in spinal cord-injured patients, demonstrating lower rates of symptomatic urinary tract infection and upper tract deterioration with suprapubic drainage (Ku et al. 2005; Esclarin de Ruz et al. 2000). To minimize catheter-related morbidity, scheduled catheter changes should be conducted on a monthly basis (Russo 2000). Chronic suppressive antibiotics are not recommended in catheterized patients but short-course antibiotic therapy may be used at the time of catheter exchange.

13.9.3

Urinary Retention After Prostatectomy

Prostate cancer treatment with curative intent can also predispose to urinary retention. Although the true incidence of bladder neck contracture following radical prostatectomy is not known, 1.3%–27% of patients will develop symptomatic BNC requiring treatment (Anger et al. 2005). Surgical technique remains a critical determinant of BNC development; however, risk factors for microvascular disease such as smoking, hypertension, and diabetes mellitus also appear to play a role (Borboroglu et al. 2000). Simple dilation appears to be effective; however, some authors question the long-term patency rates with such treatment. Transurethral incision of the contracture using cold knife, electrocautery, or the holmium:YAG laser is the most commonly recommended treatment for severe BNC and those cases involving urinary retention (Anger et al. 2005; Salant et al. 1990). Great care must be taken when performing transurethral incision since deep incision may cause sphincteric damage and, in turn, stress urinary incontinence.

13.9.4

Urinary Retention After Brachytherapy

Urinary retention affects 1.5%–22% of men within a median of 2 months following prostatic brachytherapy (Stone and Stock 2002; Flam et al. 2004). Identified preimplant risk factors include an International Prostate Symptom Score above 20 and a prostate volume larger than 35 cm³ (Terk et al. 1998; Gelblum et al. 1999). Attempts to reduce the risk of urinary retention with prophylactic α -adrenergic blockade (Flomax) have thus far been unsuccessful (Elshaikh et al. 2005).

The majority of cases respond to conservative measures such as catheter drainage plus or minus α -blockade, those that do not require TURP. According to a recent meta-analysis, up to 8.7% of brachytherapy patients undergo TURP after implantation; however, large contemporary series report a lower rate of 1.1%–2% (Stone and Stock 2002; Allen et al. 2005; Kollmeier et al. 2005). Urinary incontinence, while uncommon after TURP performed for BPH (1%–5%), is reported in up to 70% of brachytherapy patients who undergo TURP (Foote et al. 1991; Hu and Wallner 1998). The results of more recent series suggest the rate of post-TURP incontinence is 0%–18% (Stone and Stock 2002; Kollmeier et al. 2005). Radiation dose, pre-implantation prostate volume, and hormonal therapy do not appear to be predictive of subsequent incontinence; however, TURP performed more than 2 years after implant does appear to be a risk factor.

13.10 Respiratory Complications

13.10.1

Pulmonary Emboli

In urologic malignancies the primary respiratory complication is fatal postoperative pulmonary emboli (PE) (Fig. 13.7). The incidence of deep venous thrombosis (DVT) and PE following urologic surgery in patients without prophylaxis has been reported to be as high as 50% and 22%, respectively (Allgood et al. 1970; Mayo et al. 1971). With the use of intermittent pneumatic compression devices, the incidence of PE has decrease to 2% (Igel et al. 1987; Leandri et al. 1992; Lepor and Kaci 2003; Soderdahl et al. 1997). Scardino and others at Baylor College of Medicine published an extensive

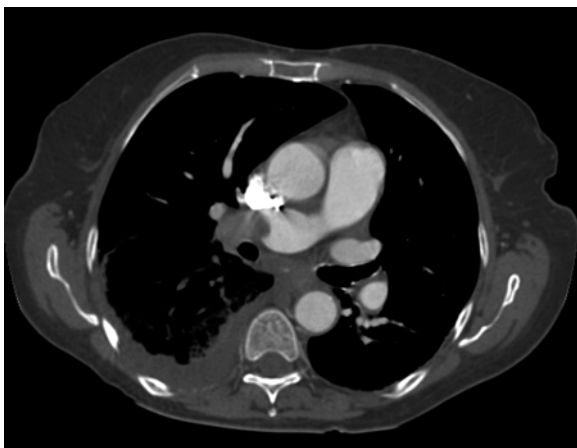


Fig. 13.7. Pulmonary embolism. Contrast-enhanced CT demonstrating pulmonary embolism as large filling defect within proximal right pulmonary artery in patient with renal cell carcinoma

review of published series reporting the perioperative morbidity of radical prostatectomy (Dilliogluligil et al. 1997). In a combined series of nearly 1,300 patients, the mortality rate was 1.18%, with a PE incidence of 2.76%.

Controversy exists regarding the optimal DVT prophylaxis for GU patients. The University College of Dublin forwarded questionnaires to all urology residency programs in Ireland, the United Kingdom, and the United States regarding the current practice with respect to thromboprophylaxis (Galvin et al. 2004). Among the three countries, there was no difference in the use of nonpharmacological thromboprophylaxis, with about 75% using either intermittent pneumatic compression devices or support stockings. However, just 24% of American urologists use pharmacological thromboprophylaxis, such as conventional or low-molecular-weight heparin, in contrast to 100% of British urologists.

There continues to be no consensus in regards to the optimal DVT prophylaxis, though the minimum would be the use of support stockings with either the addition of compression devices or pharmacological thromboprophylaxis.

13.10.2

Bleomycin Toxicity

Testicular cancer is unique in that cure often requires an integration of chemotherapy and surgery. Treatment of widely metastatic disease consists of cisplatin-based chemotherapy, typically with three or four courses of cisplatin, etoposide, and bleomycin. Those patients not achieving radiographic response with residual retroperitoneal disease typically undergo post-chemotherapy surgery. It is in this setting that the urologist must confront the potential postoperative pulmonary toxicity related to bleomycin use.

Bleomycin exerts its cytotoxic effect by induction of free oxygen radicals, resulting in DNA breaks and cell death, as well as the inhibition of tumor angiogenesis. Due to the lack of the bleomycin-inactivating enzyme, bleomycin hydrolase, in the lungs and skin, bleomycin-induced toxicity occurs predominately in these organs. A multi-institutional study involving 812 testis cancer patients performed serial pulmonary function testing to define pulmonary toxicity related to bleomycin administration (de Wit et al. 2001). This study found a median acute decline in carbon monoxide diffusion capacity (DCLO) of 19% in patients who received a cumulative dose of 270 units. Chronic decline in DCLO has not been shown. The toxic death rate at this dose is less than 0.2%, with no significant impairment in long-term pulmonary function. At doses of 360 units, the toxic death rate increased to 1%–2%.

Prior bleomycin exposure has been associated with an increased risk of postoperative pulmonary compli-

cations including fatal acute respiratory distress syndrome (ARDS). In the 1980s and early 1990s at our institution, the postoperative management of such patients involved the judicious administration of postoperative fluid preferring oliguria and prerenal creatinine rise to the potential of ARDS. With clinical experience, improved surgical technique with decreased blood loss and operative time, we no longer limit post-operate hydration. Massively obese patients, those who have received salvage chemotherapy, or have extensive surgical dissections are at higher risk of postoperative pulmonary complications and we would recommend judicious fluid administration with monitoring of volume status.

13.10.3

Pulmonary Metastases

On rare occasions, patients with germ cell tumors may present with respiratory compromise secondary to massive pulmonary metastases. In this circumstance, systemic chemotherapy is initiated on an emergent basis in lieu of radical orchiectomy. Although most patients would likely tolerate a primary orchiectomy, respiratory failure represents the most immediate threat to life and warrants directed therapy as such. Radical orchiectomy is generally performed within a few weeks of initiating chemotherapy.

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